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I consider Chemistry – An Asian Journal to be one of the finest journals of Chemistry. It has surpassed all expectations. In a very short time, it has attained the quality and impact equivalent to the very best journals that we have. It has also given a special place for Asian chemistry because through this journal chemistry in Asia can shine in the world of chemistry. I am proud to be associated with this journal and I am sure that it will reach even greater heights in the years to come.

C.N.R. Rao

Chairman of the Editorial Board

Ryoji Noyori
Nagoya University and RIKEN, Saitama, Japan

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Noyori acquired bachelor's and master's degrees from Kobe University (Japan) and completed his PhD there in 1967, under the supervision of H. Nozaki, on the first example of organometallic asymmetric catalysis. He was then appointed associate professor at Nagoya University, and only later, in 1969, had the opportunity to carry out postdoctoral research with E. J. Corey (Harvard University, USA). Back in Nagoya he was promoted to professor in 1972 and has remained faithful to this institution while serving as president of RIKEN, since 2003. His work on asymmetric hydrogenation, for example with binap complexes, earned him the Nobel Prize in 2001, together with W. S. Knowles and K. B. Sharpless.

Fürstner completed his PhD in 1987 at the Technical University of Graz with H. Weidmann and completed his habilitation there in 1992, following a postdoctoral fellowship with W. Oppolzer (University of Geneva). He has been a group leader at the Max Planck Institute at Mülheim since 1993 and has been a director there since 1998. He carries out pioneering work at the interface between organometallic chemistry and organic synthesis, in particular alkene and alkyne metathesis and its application to the total synthesis of complex natural products, such as carbohydrates and alkaloids.
Exploring New Superconductors and Other Supermaterials

Hideo Hosono
Tokyo Institute of Technology
(Yokohama, Japan)

The research of H. Hosono is devoted to inorganic solid-state materials chemistry, especially transparent oxide semiconductors, which are used in flat-panel displays, and new superconductors: He introduced iron into the family of oxide superconductor components. Hosono earned a PhD from Tokyo Metropolitan University under the guidance of H. Kawazoe in 1982 and joined the faculty of Nagoya Institute of Technology. In 1999, he became a professor at the Tokyo Institute of Technology.

25 Years of Membrane Protein Structures: Successes and Open Questions

Hartmut Michel
Max-Planck-Institut für Biophysik
(Frankfurt/Main, Germany)

In 1988, Hartmut Michel received the Nobel Prize in Chemistry together with J. Deisenhofer and R. Huber for the determination of the three-dimensional structure of a photosynthetic reaction center. Michel studied biochemistry at the Universität Tübingen (Germany) and in 1977 completed his PhD with D. Oesterhelt at the Universität Würzburg (Germany) on proton gradients at the cell membranes of halobacteria. Shortly afterwards he began attempts to crystallize membrane proteins, in which he succeeded in 1979. He moved with Oesterhelt to the Max Planck Institute of Biochemistry (Martinsried, Germany) and in 1981 succeeded in crystallizing a photosynthetic reaction center. In 1987 he became director at the MPI of Biophysics (Frankfurt/M.).
Olefin Polymerization: FI Catalysts for the Creation of Value-Added Olefin-Based Materials

Terunori Fujita
Mitsui Chemicals Inc. Research Center
(Chiba, Japan)

T. Fujita graduated from Hokkaido University in 1982 and earned a PhD in 1988 in supramolecular chemistry from the Louis Pasteur University in Strasbourg under the supervision of Jean-Marie Lehn. In 1982 he joined Mitsui Petrochemical Industries (now Mitsui Chemicals). In 2001 he was appointed a Mitsui research fellow for his contributions to the development of new olefin polymerization catalysts, now known as FI catalysts. He is currently a board director and the Center Executive of the company’s research center. Fujita’s research interests have focused on the synthesis of valuable organic materials by means of homogeneous and heterogeneous catalysis and, more recently, on the development of high-performance olefin polymerization catalysts for the creation of new value-added olefin-based materials.

Cross-Coupling Reactions of Organoboranes: An Easy Way for C—C Bonding

Akira Suzuki
Hokkaido University
(Sapporo, Japan)

Suzuki received his doctorate in 1959 at Hokkaido University, Sapporo (Japan) and was, after a research stay with H. C. Brown (Purdue) in the late 1960s, a professor there from 1965 until 1994. Towards the end of the 1970s he was able to show that organoboron compounds can be coupled with vinyl and aryl halides under basic conditions and palladium catalysis. Together with Richard F. Heck and Ei-ichi Negishi, this discovery earned him the Nobel Prize in Chemistry in 2010.
Molecular Recognition in Chemical and Biological Systems

François Diederich  
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Eidgenössische Technische Hochschule  
(Zürich, Switzerland)

Diederich completed his PhD in 1979 at the University of Heidelberg (Germany) with H. A. Staab. He carried out postdoctoral research at the University of California in Los Angeles (UCLA; USA) and at the Max Planck Institute for Medicinal Research in Heidelberg. After completing his habilitation in 1985 he returned to UCLA, and in 1992 he joined the ETH Zürich. He has been the chairman of the editorial board of Angewandte Chemie since 2004. Besides the areas of molecular recognition in chemistry and biology, supramolecular nanochemistry, the chemistry of synthetic fullerenes, and novel materials from carbon-rich acetylene derivatives, Diederich's research group is also interested in medicinal chemistry eg. of antimalarial drugs.

Total Synthesis of Natural Products and Development of Synthetic Methodologies

Tohru Fukuyama  
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Graduate School of Pharmaceutical Sciences (University of Tokyo, Japan)

After graduation from Nagoya University, Fukuyama obtained his PhD in 1977 under the direction of Y. Kishi (Harvard University). After a postdoc time there, he joined the faculty of Rice University (Houston, TX) and became a professor of pharmaceutical sciences at the University of Tokyo in 1995. His research is devoted to the total synthesis of complex natural products.
Homolytic C—H Bond Activation: Experimental and Theoretical Insights/ Research in Germany

Helmut Schwarz  
helmut.schwarz@mail.chem.tu-berlin.de  
Technische Universität Berlin  
(Berlin, Germany)

After training as a chemical technician, Schwarz remained true to the Technical University of Berlin: He earned his doctorate and habilitation under the guidance of natural-products chemist F. Bohlmann and is currently a professor of Organic Chemistry there. He held numerous visiting appointments in Great Britain, Switzerland, Israel, France, Japan, and Australia. His research is inextricably linked to mass spectrometry and gas-phase chemistry, especially the activation of C-C and C-H bonds and the role of metals in catalysis. Since 2008, Helmut Schwarz has served as president of the Alexander von Humboldt Foundation, which promotes academic cooperation between excellent scientists and scholars from Germany and abroad.

Click Chemistry Keeps Evolving — Destinations Unknown

Barry Sharpless  
sharples@scripps.edu  
The Scripps Research Institute  
(La Jolla, USA)

The research of Barry Sharpless is focused on homogeneous oxidation catalysts, for which he received the Nobel prize in chemistry in 2001. His group also works on asymmetric processes and has developed the concept of click chemistry. Sharpless studied at Dartmouth College and Stanford University where he earned a PhD under the guidance of E. E. van Tamelen in 1968. He carried out post-doctoral research at Stanford (with J. P. Collman) and Harvard University (with K. Bloch) before joining the faculty of the Massachusetts Institute of Technology from 1970—90, interrupted by an appointment at Stanford in the late 1970s. Since 1990, he is a Professor at The Scripps Research Institute.
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Hartmut Michel was awarded the Nobel prize for the crystallization and crystallographic characterization of the photosynthetic reaction center of the purple bacterium Rhodopseudomonas viridis. His research increased the general understanding of the mechanisms of photosynthesis, revealed similarities between the photosynthetic processes of plants and bacteria and established a methodology for crystallizing membrane proteins.
The Photosynthetic Reaction Center from the Purple Bacterium *Rhodopseudomonas viridis* (Nobel Lecture)**

By Johann Deisenhofer* and Hartmut Michel*

In our lecture we first describe the history and methods of membrane protein crystallization, before we show how the structure of the photosynthetic reaction center from the purple bacterium *Rhodopseudomonas viridis* was solved. The structure of this membrane protein complex is then correlated with its function as a light-driven electron pump across the photosynthetic membrane. Finally, we draw conclusions on the structure of the photosystem II reaction center of plants and discuss the aspects of membrane protein structure. Sections 1 (crystallization), 4 (conclusions on the structure of photosystem II reaction center and evolutionary aspects) and 5 (aspects of membrane protein structure) were presented and written by H. M., sections 2 (determination of the structure) and 3 (structure and function) by J. D. We have arranged the manuscript in this way in order to facilitate continuous reading.

1. The Crystallization

1.1. The Background

As in many instances of new scientific developments and technical inventions a chance observation initiated a series of experiments, which ultimately resulted in the elucidation of the three-dimensional structure of a photosynthetic reaction center. In August 1978 I accidently observed the formation of solid, most likely glass-like aggregates, when lipid-free bacteriorhodopsin prepared according to the method of Happe and Overath[11] (1976) was stored in the freezer. These aggregates are shown in Figure 1A. From that time on I was convinced that it should be possible not only to produce these solid bodies but also to prepare three-dimensional crystals. The availability of well-ordered three-dimensional crystals is a prerequisite for a high resolution X-ray crystallographic analysis, which—despite the progress made by Henderson and Unwin[21] (1975) with electron microscopy and electron diffraction on bacteriorhodopsin—was, and still is the only way to obtain a detailed structural knowledge of large biological macromolecules.

At the time I was working at the University of Würzburg as a post-doc in Dieter Oesterhelt’s lab, who, in collaboration with Walter Stoeckenius, had discovered bacteriorhodopsin[19] and was the first to propose its function.[6] My intention to try to produce well-ordered three-dimensional crystals of bacteriorhodopsin received his immediate support. It turned out that he had already tried to crystallize a modified form of bacteriorhodopsin from organic solvents.

Bacteriorhodopsin, the protein component of the so-called purple membrane, resembles the visual pigment rhodopsin and acts as a light energy converting system. It is part of a simple “photosynthetic” system in halobacteria, and is an integral membrane protein, which forms two-dimensional crystals in the purple membrane. At that time the general belief was that it was impossible to crystallize membrane proteins in three dimensions. With the exception of bacteriorhodopsin there was no information about the three-dimensional structure of membrane proteins, which might

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are embedded into the electrically insulating lipid bilayers. Difficulties are encountered in the handling of membrane proteins because of the amphipathic nature of their surface. It is hydrophobic where the membrane proteins have contact with the alkane chains of the lipids, and it is hydrophilic where the membrane proteins have contact with the aqueous phase (on both sides of the membrane) or with the polar head-groups of the lipids (see Fig. 2). As a result membrane proteins are not soluble in aqueous buffers or in organic solvents with low dielectric constants. In order to solubilize membrane proteins one has to add detergents. Detergents are amphiphilic molecules which form micelles above a certain concentration, the so-called critical micellar concentration. The detergent micelles take up the membrane proteins and shield the hydrophobic parts of the surface of the membrane protein from contact with water. A schematic drawing of a biological membrane and its solubilization with detergents is presented in Figure 2. The membrane protein in the detergent micelle then has to be purified by chromatographic methods.

Once the protein has been isolated and is available in large quantities, one can try to crystallize it. For membrane proteins, which are merely anchored in the membrane, the most promising approach is to remove the membrane anchor by proteases or to use genetically modified material where the part of the gene coding for the membrane anchor has been deleted. Four examples of highly resolved structures of the hydrophilic domains have already been reported: cytochrome b₅₆₃ [90], hemagglutinin [100] and neuraminidase [114] from influenza virus and the human class I histocompatibility antigen, HLA-A₂ [112].

There are two possibilities for generating true three-dimensional crystals of really integral membrane proteins:

1) One could think of forming stacks of two-dimensional crystals of membrane proteins. Perpendicular to the membrane the two-dimensional crystals must be ordered with respect to translation, rotation and orientation during or after their formation. In most cases the lipids might still be

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1.2. A More Systematic Approach

Based on the properties of membrane proteins outlined below, a new strategy was developed. Membrane proteins have provided insights into their various functions, e.g. as carriers, energy converters, receptors or channels.

In our first experiments we tried to decrease the negative surface charge of purple membrane by the addition of long chain amines, and, by subsequent treatment with Triton X100, a detergent, to facilitate rearrangement of the bacteriorhodopsin molecules, which were partly solubilized by the detergent. This procedure may be a way (see Fig. 3) to obtain the type I crystals described below. Within four weeks we obtained the "needles" illustrated in Figure 1B. Electronmicroscopic studies carried out in collaboration with Richard Henderson in Cambridge showed that the "needles" were a new two-dimensionally crystalline membrane form of bacteriorhodopsin. In this new form the membranes are rolled up like tobacco leaves in a cigar [71].

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Fig. 1. Optical micrographs showing crystals and aggregates of bacteriorhodopsin and the photosynthetic reaction center from Rhodopsseudomonas viridis: A) "glass-like" aggregates of bacteriorhodopsin obtained after freezing of lipid-free bacteriorhodopsin; B) rolled up sheets of the two-dimensionally crystalline orthorhombic form of purple membrane (after Michel and Oesterhelt [3]); C) needle-like crystals of bacteriorhodopsin obtained with sodium phosphate as precipitant; D) cube-like crystals of bacteriorhodopsin obtained with ammonium sulfate as precipitant; E) filamentous aggregates of bacteriorhodopsin and a few cubes (arrows) obtained with ammonium sulfate as precipitant (after Michel [4a]); F) hexagonal columns of bacteriorhodopsin obtained in the presence of 3% heptane-1,2,3-triol with ammonium sulfate as precipitant; G) star-like crystals of the reaction center obtained within 2 days (starting conditions: 1 mg protein/ml, 3% heptane-1,2,3-triol, 1.5 mM ammonium sulfate) by vapor diffusion against 3 mM ammonium sulfate (after Michel [4b]); H) tetragonal crystals of the reaction center obtained within 3 weeks (starting conditions as under G) by vapor diffusion against 2.4 mM ammonium sulfate (after Michel [4b]). In all photographs the bar indicates 0.1 mm.

Fig. 2. Schematic drawing of a biological membrane consisting of a lipid bilayer in which membrane proteins are embedded (top), and its solubilization by detergents (bottom). The hydrophilic part of the membrane protein surface is indicated by broken lines (modified after Michel [8]).
present in the form of bilayers and compensate the hydrophobicity of the intramembranous protein surface. Hydrophobic and polar interactions would stabilize the crystals in the membrane planes, whereas polar interactions would dominate in the third dimension (Fig. 3, left). In a reasonable crystallization procedure one would have to increase both types of interaction at the same time. This seems to be difficult to achieve.

2) The alternative is to crystallize the membrane proteins within their detergent micelles. The crystal lattice will be formed by the membrane proteins via polar interactions between the polar parts of the surface. Figure 3 (right) shows one example of such a crystal. It is immediately clear that membrane proteins with large extramembranous domains should form this type of crystal much easier than those with small polar domains. The size of the detergent micelle plays a crucial role. A large detergent micelle might prevent the required close contact between the polar surface domains of the membrane proteins. One way to achieve a small detergent micelle is to use small linear detergents like octyl glucopyranoside. However, for membrane biochemists, a general experience is that membrane proteins in micelles formed by a detergent with a short alkyl chain are not very stable. An increase in length of the alkyl chain by one methylene group frequently leads to an increase in stability by a factor of two to three. One therefore has to find a compromise.

The advantage of the type II crystals is that basically the same procedures to induce supersaturation of the membrane protein solution can be used as for soluble proteins, namely vapor diffusion or dialysis with salts or polymers like polyethylene glycol as precipitating agents. Frequently a viscous detergent phase is formed, which seems to consist of precipitated detergent micelles (see, e.g., Ref. [13]). This phase separation is a serious problem. Membrane proteins are enriched in the detergent phase, and frequently undergo denaturation. In several examples crystals which were already formed are redissolved.

Bacteriorhodopsin, solubilized in octyl glucopyranoside, forms needle-like crystals (Fig. 1 C) when phosphate is used as precipitant (Fig. 1 C) and cubic crystals when ammonium sulfate[13] (Fig. 1 D) is used. The cubic crystals are not very stable, and transform into hairy, thread-like material (Fig. 1 E) after several weeks.14 In this hairy material bacteriorhodopsin probably forms membranes again.

OmpF-porin, an outer membrane protein from Escherichia coli, was also crystallized — after solubilization in octyl glucopyranoside — by Garavito and Rosenbusch.14 We received knowledge of this parallel development when D. Oesterhelt and J. P. Rosenbusch met in China at the end of 1979.

1.3. The Improvement

My opinion regarding the lack of final success with bacteriorhodopsin was always that the detergent micelles were still too large. The use of even smaller detergents was impossible due to insufficient stability of the bacteriorhodopsin in detergents with a shorter alkyl chain or a smaller polar head group. For several reasons, one way out was to add small amphiphilic molecules:14a,14i (i) these molecules might displace detergent molecules which are too large to fit perfectly into the protein’s crystal lattice in certain positions. (ii) The small amphiphilic molecules are too small to form micelles themselves, but they are incorporated into the detergent micelles. These mixed micelles are smaller than the pure detergent micelles and the curvature of their surface is different. As a result the protein’s could come closer together. (iii) Their polar head group is smaller than that of the detergent and less of the protein’s polar surface would be covered by the polar part of the mixed small amphiphile/detergent micelle.

I had a look through the major chemical companies’ catalogues and ordered nearly everything which was polar at one end and hydrophobic at the other. In addition I synthesized about 20 amphiphilic compounds, mainly alkyl polyols and alkyl N-oxides. These compounds were added during our attempts to crystallize bacteriorhodopsin. Several of the compounds had the effect that hexagonal columns were obtained (see Fig. 1 F), whereas cubes (Fig. 1 D) had been obtained without the additives. The most effective compound was heptane-1,2,3-triol, but it had a slightly denaturing effect on bacteriorhodopsin. The diffraction quality of the bacteriorhodopsin crystals was improved: Using synchrotron radiation H. Bartunik, D. Oesterhelt and I were occasionally able to achieve a resolution of 3 Å, but only in one direction.

1.4. The Turn to Classical Photosynthesis

Frustrated from the failure to make a final breakthrough with bacteriorhodopsin, which was partly due to the absence of large extramembranous domains in this protein, I looked for more promising membrane proteins for crystallization. I chose the photosynthetic reaction centers from the purple bacteria Rhodopseudomonas viridis and Rhodopseudomonas viridis and the light-harvesting chlorophyll a/b protein from spinach. I was influenced by the fact that these proteins (or protein-complexes) were said to be already part of a two-dimensional crystalline array in their native environment. As additional benefits they were available in large quantities, could easily be isolated, were colored and denaturation of the proteins was indicated by color changes.

I learnt about the Rhodopseudomonas viridis system when Ernst Wehrli from the ETH Zürich presented the results of electron microscopic studies during a workshop at Burg Gemen, Germany, in June 1979 (see Ref. [15]). Initially, I received some isolated photosynthetic membranes from him in December 1980. At that time I had moved with D.
Oesterhelt to the Max-Planck-Institut für Biochemie at Martinsried near Munich and I was just back from a stay at the MRC in Cambridge where we had carried out X-ray diffraction experiments on the bacteriorhodopsin crystals. We isolated the reaction center using hydroxyapatite chromatography according to a procedure published by Clayton and Clayton in 1978.[16] We tried to crystallize the isolated reaction centers, but without success. I developed a new procedure of isolation using only molecular sieve chromatography and tried again, and met with immediate success. The conditions were nearly identical to those found to be optimal for bacteriorhodopsin. The exception was that I could use N,N-
dimethyldecylamine N-oxide as detergent instead of octyl gluco.pyranoside (see Fig. 4). In the presence of 3/

![Fig. 4. Structural formulas of commonly used detergents: octyl-β-D-glucopyranoside, N,N-dimethyldecylamine N-oxide, decanoyl-N-methylglucamide]  

heptane-1,2,3-triol (high melting point isomer) and 1.5 to 1.8 M ammonium sulfate, star-like crystals were obtained upon vapor diffusion against 2.5 to 3 M ammonium sulfate in two days; more regular tetragonal columns with a length of up to 2 mm were formed upon vapor diffusion against 2.2 to 2.4 M ammonium sulfate in two to three weeks (see Figs. 1 G, 1 H). The much smaller polar head group of N,N-dimethyldecylamine N-oxide is certainly of importance. Unfortunately, this detergent denatures bacteriorhodopsin. D. Oesterhelt generously considered the reaction center as my project.

The crystals turned out to be of excellent quality from the beginning. After a scaling-up of the isolation procedure, a continuous supply of crystals was guaranteed. Initially with the help of Wolfram Bode and Robert Huber, I could now start collecting the X-ray data. Figure 5 shows a rotation photograph similar to that used for the data collection.

![Fig. 5. X-ray diffraction pattern of a single crystal of the reaction center (1 rotation). Exposure time: 20 h, CuKα radiation, crystal to film distance: 100 mm. The arrow indicates 3.0 Å resolution (after Michel [4b]).]

2. Determination of the Structure

In spring 1982 I (J. D.) joined H. M. in order to determine the three-dimensional structure of the reaction center. The tetragonal crystals have unit cell dimensions of a = b = 223.5 Å, c = 113.6 Å, and the symmetry of space group P4₁2₁2₁.[4,17] As it turned out, there is one reaction center with a molecular weight of 145 000 Daltons in the asymmetric unit.

2.1. Collection of X-ray Reflection Intensity Data

For data collection we used the rotation method with a rotating anode X-ray generator as the source, and photographic film as the detector.[17] The large unit cell of the reaction center crystals, in combination with the resolution limit of the diffraction pattern at 2.9 Å, limited the rotation interval per film exposure to 0.5°, so that more than two thirds of the reflections on any given film were only partially recorded. However, the long lifetime of the crystals in the X-ray beam at about 0°C, and their positional stability allowed to add up partially recorded reflections from successive exposures, so that their treatment did not present a serious problem. Nevertheless, it took about three to four months to collect a complete data set. Data collection for the heavy atom derivatives was speeded up by choosing a rotation interval of 0.6° per exposure. A later re-collection of the native data set at the HASYLAB facilities of DESY in Hamburg was carried out at 2.3 Å resolution in rotation intervals of 0.4° by Irmgard Sinning, Gerhard Schertler, and H. M.

The most tedious and time consuming task in this type of data collection was the processing of films. Kunio Miki and later Otto Epp provided invaluable help during that period of the work. We used the computer programs FILME[18,19] and OSC[20,21] for film evaluation, and PROTEIN (principal author: W. Steigemann) for scaling and merging data.
2.2. Solution of the Phase Problem

To solve the phase problem for the crystal structure of the reaction center we used the method of isomorphous replacement with heavy atom compounds. The experimental part was performed by H. M., the film evaluation and data analysis by myself with support from Kunio Miki and Otto Epp.

In order to find the heavy atom derivatives, crystals were soaked for three days in 1 mM solutions of the respective heavy atom compounds in a soak buffer similar to the mother liquor. A number of compounds like K₂PtBr₄, K₂Pt(CN)₄, K₂Hg(CN)₂, K₂HgCl₄ and EuCl₃ could not be used since they induced the separation of the soak buffer phase into a viscous detergent phase and an aqueous phase. It was established from the beginning that X-ray diffraction no longer occurred on using large heavy atom compounds like \((\text{C}_6\text{H}_5)_3\text{PbNO}_3\) or \(\text{C}_6\text{H}_5\text{HgCl}\), whereas the smaller homologues \((\text{CH}_3)_3\text{PbCl}\) or \(\text{C}_6\text{H}_5\text{HgCl}\) reduced the diffraction to about 6 Å resolution. However, after additional purification of the reaction centers prior to the crystallization the diffraction quality of the crystals was unchanged by the small heavy atom compounds. One compound (K₂AuCl₄) caused a shrinkage of the c-axis. Rotation photographs \((\theta)\) showing a large part of the \(1_k_l\) lattice plane were taken and inspected visually for changes in the diffraction pattern. For promising candidates, ca. 50% complete data sets were collected and evaluated.

On average, each heavy atom derivative had nine heavy atom binding sites. The major binding sites were found with the automatic search procedure in the PROTEIN program package. Using five different heavy atom derivatives, we could calculate phases to 3.0 Å resolution, and an electron density map. Phases and map were further improved by solvent flattening.

2.3. Model Building

Map interpretation and model building was done in three stages: First the prosthetic groups in the reaction center were identified. We found the four heme groups, the four bacteriochlorophyll-b molecules, the two bacteriopheophytin-b molecules, and one quinone molecule. Next, the polypeptide chains were built with polyalanine sequence — except in the amino terminal regions of the subunits L, M, and cytochrome where partial amino acid sequences were known and could be used to distinguish between the subunits. At that stage, some use was made of the local symmetry of the subunits L and M. Finally, as the gene sequences of the reaction center subunits were determined the model of the protein subunits was completed. The sequence information not only led to an overall verification but also to a number of minor corrections of the polypeptide backbone model, since in the previous model building stage the electron density was not always clear enough to allow determination of the correct number of amino acids.

Our tools for model building were interactive graphics display systems: a Vector General 3400 system (black and white), and later an Evans & Sutherland PS 300 system (color). For both systems we used Alwyn Jones' program package FRODO. The model library of this package was extended to include bacteriochlorophyll-b, bacteriopheophytin-b, menaquinone-7, and ubiquinone-1. Frequent use was made of the real-space refinement facility in FRODO which allowed correct incorporation of long stretches of helical structure into the electron density.

2.4. Model Refinement

The reaction center model, with about half of the side chains of the cytochrome subunit still missing, already had the rather low crystallographic R-value of 0.359 at 2.9 Å resolution \((R = \Sigma(\|F_{calc}\| - |F_{obs}|)/\Sigma|F_{obs}|)\). and \(F_{calc}\) are observed and calculated structure factors, respectively). Crystallographic refinement of the model was started at 2.9 Å resolution, and continued at 2.3 Å resolution. The program packages used for refinement were PROTEIN, ERF, TNT, and again FRODO.

As a result of the refinement the R-value was brought down to 0.193 for 95 762 unique reflections at 2.3 Å resolution, the refined model consists of 10 288 non-hydrogen atoms. Errors in the initial model, e.g. peptide groups and side chains with wrong orientations, were removed. New features were added to the model: a partially ordered carotenoid molecule, a ubiquinone in the partially occupied \(Q_b\) binding pocket, a complete detergent molecule (LDAO, see Fig. 4), a candidate for a partially ordered LDAO or similar molecule, seven candidates for negative ions, and 201 ordered water molecules. The upper limit of the mean coordinate error was estimated to be 0.26 Å. A detailed description of refinement and refined model of the photosynthetic reaction center from Rhodopseudomonas viridis will be given elsewhere (J. Deisenhofer, O. Epp, I. Sinning, H. Michel, to be published).

3. Structure and Function

3.1. Structure Overview

An overall view of the structure of the photosynthetic reaction center from Rhodopseudomonas viridis is shown in Figure 6. It is a complex of four protein subunits, and of 14 cofactors. The protein subunits are called H (heavy), M (medium), L (light), and cytochrome; the names H, M, and L were chosen according to the apparent molecular weights of the subunits, as determined by electrophoresis. The core of the complex is formed by the subunits L and M, and their associated cofactors: four bacteriochlorophyll-b (BChl-b) molecules, two bacteriopheophytin-b (BPh-b) molecules, one non-heme iron ion, two quinone molecules, one carotenoid molecule. Structural properties, e.g. the hydrophobic nature of the protein surface, and functional considerations strongly indicate that the subunits L and M span the bacterial membrane. This aspect of the structure will be discussed in Section 5. Each of the subunits L and M contains five membrane spanning polypeptide segments, folded into long helices. The polypeptide segments connecting the transmembrane helices form flat surfaces parallel to the membrane surfaces.

The H subunit contributes another membrane spanning helix with its N-terminus near the periplasmic membrane surface. The C-terminal half of the H subunit forms a globular domain that is bound to the L–M complex near the cytoplasmic membrane surface. On the opposite side of the membrane the cytochrome subunit with its four covalently bound heme groups is attached to the L–M complex. Both the cytochrome subunit and the globular domain of the H subunit have surface properties typical for water soluble proteins.

The total length of the reaction center, from the tip of the cytochrome to the H subunit is about 130 Å. The core has an elliptical cross section with axes of 70 Å and 30 Å.

The photosynthetic reaction centers from purple bacteria are the best characterized among all photosynthetic organisms (reviews: Refs. [32, 33]). All of them contain the three subunits H, M, and L; some bacteria lack the tightly bound cytochrome subunit. An example of a reaction center without a bound cytochrome subunit is that from Rhodobacter sphaeroides, which was also crystallized,[34, 35] its structure has been shown to be very similar to the reaction center of Rhodopseudomonas viridis.[36, 37]

3.2. Subunit Structure

The folding of the polypeptide chains of the four reaction center subunits is shown schematically in Figure 7. As mentioned above, major elements of secondary structure in the subunits L and M are the five membrane spanning helices. A comparison of the polypeptide chain folding in both subunits reveals a high degree of similarity. Structurally similar segments include the transmembrane helices and a large fraction of their connections. In total, 216 α-carbons from the M-subunit can be superimposed onto corresponding α-carbons of the L-subunit with an r.m.s. deviation of only 1.22 Å. The superposition of the subunits is achieved by a rotation of ca. 180° about an axis running perpendicular to the membrane surface; we call this axis the central local symmetry axis. Table 1 lists the helices in both subunits, and Table 2 lists the structurally similar regions in both subunits. Besides the transmembrane helices, called LA, LB, LC, LD, LE, and MA, MB, MC, MD, ME, with lengths between 21 and 28 residues, there are shorter helices in the connecting segments, notably helix de (between transmembrane helices D and E), and helix cd. Subunit M (323 residues) is 50 residues longer than L (273 residues). The insertions in M,
Fig. 7. Stereoview of the smoothed backbone representations of the protein subunits. The secondary structure is indicated in color: yellow, no apparent secondary structure; red, transmembrane helices; purple, other helices; blue, antiparallel β-sheets. a) Cytochrome (with the four heme groups); b) L-subunit; c) M-subunit; d) H-subunit. N-termini are marked blue, C-termini are marked red.

Table 1. Helical segments in subunits L and M.

<table>
<thead>
<tr>
<th>Helix</th>
<th>Segment (length)</th>
<th>Subunit L</th>
<th>Segment (length)</th>
<th>Subunit M</th>
</tr>
</thead>
<tbody>
<tr>
<td>transmembrane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>L33–L53 (21)</td>
<td>M52–M76 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>L44–L111 (28)</td>
<td>M111–M137 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>L116–L139 (24)</td>
<td>M143–M166 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>L171–L198 (28)</td>
<td>M198–M223 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>periplasmic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cd</td>
<td>L152–L162 (11)</td>
<td>M179–M190 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ect</td>
<td>L259–L267 (9)</td>
<td>M292–M298 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cytoplasmic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M241–M254 (14)</td>
<td></td>
</tr>
</tbody>
</table>

The H-subunit with 258 residues can be divided into 3 structural regions with different characteristics (see Fig. 7). The N-terminal segment, beginning with formylmethionine, contains the only transmembrane helix of subunit H; it consists of 24 residues (H12 to H35). Near the end of the transmembrane helix the sequence shows seven consecutive charged residues (H33 to H39). Residues H47 to H53 are disordered in the crystal, so that no significant electron density can be found for them.

Following the disordered region the H chain forms an extended structure along the surface of the L–M complex, apparently deriving structural stability from that contact. The surface region contains a short helix and two two-stranded antiparallel β-sheets.

The third structural segment of the H-subunit, starting at

about H105 forms a globular domain. This domain contains an extended system of antiparallel and parallel β-sheets between residues H134 and H203, and an α-helix (residues H232 to H248). The β-sheet region, the only larger one in the whole reaction center, forms a pocket with highly hydrophobic interior walls. This structural property reminds one of transport proteins like the retinol binding protein[38] and the bilin binding protein[39] however, the strand topology is different. So far, no evidence for a ligand has been found.

With 336 residues[36] the cytochrome is the largest subunit in the reaction center complex. Its last four residues, C333 to C336, are disordered. Also disordered is the lipid molecule-bound to the N-terminal cysteine residue.[40] The complicated structure of the cytochrome can be summarized as follows: The structure consists of an N-terminal segment, two pairs of heme binding segments, and a segment connecting the two pairs. Each heme binding segment consists of a helix with an average length of 17 residues, followed by a turn and the Cys-X-Y-Cys-His sequence typical for c-type cytochromes. The hemes are connected to the cysteine residues via thioether linkages. This arrangement leads to the heme planes being parallel to the helix axes. The sixth ligand to the heme iron is in three of the four cases a methionine residue within the helix. The iron of heme 4 has histidine C124, located in a different part of the structure, as a sixth ligand. The two pairs of heme binding segments, containing hemes 1 and 2, and 3 and 4, respectively, are related by a local twofold symmetry. From each pair 65 residues obey this local symmetry with an r.m.s. deviation between corresponding α-carbon atoms of 0.93 Å. The local symmetry of the cytochrome is not related to the central local symmetry.

3.3. Arrangement of Cofactors

Figure 8 shows the arrangement of the 14 cofactors associated with the reaction center protein subunits. The four heme groups of the cytochrome, numbered according to the order of attachment to the protein, form a linear chain that points to a closely associated pair of bacteriochlorophyll (BChl-b) molecules. This pair, the so-called “special pair” is the origin of the two branches of cofactors, each consisting of another BChl-b (the “accessory” BChl-b), a bacteriopheophytin-b (BPh-b), and a quinone. The non-heme iron sits between the quinones. The tetrapyrrole rings of BChl-b, BPh-b and quinone molecules approximately follow the same local symmetry that is displayed by the L- and M-chains. The branches of cofactors from the special pair to the BPh-b molecules can be clearly associated with subunits L or M, so that we speak of an L-branch and an M-branch. This is the basis for our nomenclature: BChl-b and BPh-b are called BC_{XY} and BP_{XY}, respectively, where X denotes the branch (L or M), and Y is P for “special pair” or A for “accessory”. At
the level of the quinones the situation is more complicated because the subunits interpenetrate here, and the quinone at the end of the L-branch is actually bound in a pocket of the M-subunit and vice versa. Therefore, we prefer the nomenclature Q₄ and Q₆ with Q₈ at the end of the L-branch; Q₈ is menaquinone-9, and Q₆ is ubiquinone-9.¹⁶¹ The local symmetry is violated by the phytol chains of BCHl-b and BPh-b, by the different chemical nature and different occupancy of the quinones, and by the presence of a carotenoid molecule near the accessory BCHl-b molecule of the M-branch.

3.4. Functional Overview

Our current understanding of the function of the reaction center was developed by combining structural information with information from other experimental techniques, notably spectroscopy, as described in recent reviews.¹⁴²⁻⁴⁴ Figure 9 shows a schematic view of the reaction center with its cofactors in the bacterial membrane. The special pair, P, is the starting point for a light-driven electron transfer reaction across the membrane. Absorption of a photon, or energy transfer from light harvesting complexes in the membrane puts P into an excited state, P*. From P* an electron is transferred to the bacteriochlorophyll on the L-branch (here: BP₇) with a time constant of 2.8 ps.¹⁴⁵, ¹⁴⁶ The distinction between the two bacteriochlorophyll molecules was possible because they absorb at slightly different wavelengths, and, with a knowledge of the crystal structure, linear dichroism absorption experiments could distinguish between the two chromophores.¹⁴⁷⁻⁴⁹

From BP₇ the electron is transferred to Q₈ with a time constant of ca. 200 ps. At this point the electron has crossed most of the membrane. Both these electron transfer steps function at very low temperatures (ca. 1 K) with time constants even shorter than at room temperature.¹⁵⁰, ¹⁵¹

From Q₈ the electron moves on to Q₆ in about 100 μs. The non-heme iron does not seem to play an essential role in this step.¹⁵² Q₈ can pick up two electrons and, subsequently, two protons.¹⁵³ In the Q₆H₂ state it dissociates from the reaction center, and the Q₆ site is re-filled from a pool of quinones dissolved in the membrane. Electrons and protons on Q₆H₂ (here: HQH) are transferred back through the membrane by the cytochrome b/c₁ complex. The electrons are shuttled via a soluble cytochrome c₁ to the reaction center's cytochrome from which the photo-oxidized special pair is reduced with a time constant of ca. 270 μs. This time constant increases with decreasing temperature down to ca. 100 K, and remains constant for lower temperatures. The whole process can be described as a light-driven cyclic electron flow, the net effect of which is the generation of a proton gradient across the membrane that is used to synthesize adenosine triphosphate, as described by P. Mitchell’s chemiosmotic theory. A number of still unsolved problems preclude a complete understanding of the reaction center's function. The nature of the electron transfer steps described above, and their speed and temperature dependence have not yet been explained theoretically. The first step, imposing the question of the role of the bridging BC_L₄, is a subject of fascinating debate.

One of the greatest surprises in the structure analysis was the symmetry of the core structure, raising the question of the factors leading to the use of only the L-branch of cofactors and of the significance of the apparently unused branch. Further open questions relate to electron transfer between Q₆ and Q₈, the role of the non-heme iron, and the function of Q₆ as two-electron gate and proton acceptor. Finally, the purpose of the cytochrome, as well as details of the electron transfer from the soluble cytochrome to the cytochrome in the reaction center, and within the four hemes, are yet not fully understood.

3.5. Structural Details in Relation to Function

Here I describe the arrangement of the cofactors and their environment in some detail. Observations relating to open functional questions are emphasized.

Figure 10 shows the BCHl-b ring system of the special pair, the primary electron donor of the photosynthetic light reaction. On the basis of spin resonance experiments the existence of a special pair had been postulated some time ago.¹⁴⁺ The two molecules overlap with their pyrrole rings in such a way that, when viewed in a direction perpendicular to the ring planes, the atoms of these rings eclipse each other. The orientation of the rings leads to a close proximity between the ring I acetyl groups and the Mg⁰⁺ ions; however, the acetyl groups do not act as ligands to the Mg²⁺ ions. The pyrrole rings I of both BCHl-b molecules are nearly parallel, and ca. 3.2 Å apart. Both tetrapyrrrole rings, however, are non-planar; planes through the pyrrole nitrogens of each BCHl-b form an angle of 11.3°.

The BCHl-b molecules of the special pair are arranged with a nearly perfect twofold symmetry. This is illustrated in Figure 11 which shows a view along the twofold axis.¹⁵⁺ The BCHl-b rings of the special pair are nearly parallel to this symmetry axis. Further structural elements shown in Fig-

ure 11 that obey the central local twofold symmetry are the histidine residues (L173, M200) acting as ligands to the special pair Mg$^{2+}$ ions, the rings of the accessory BChl-b molecules, the water molecules H-bonded between histidine nitrogen atoms and ring-V carbonyl groups of the accessory

BChl-b molecules, and the transmembrane helices of subunits L and M. The carotenoid molecule in contact with the accessory BChl-b (BC$_{M\alpha}$), the side chains of the accessory BChl-b molecules, and the transmembrane helix of the H-subunit are examples of structural elements that break the twofold symmetry. A more subtle deviation from symmetry is the different degree of non-planarity of the two BChl-b ring systems of the special pair. The tetrapyrrole ring of BC$_{MP}$ is considerably more deformed than that of BC$_{LP}$. This can cause an unequal charge distribution between the two BChl-b systems of the special pair, which in turn can be part of the reason for unidirectional electron transfer.$^{[36]}$

Even though the tetrapyrrole rings of the BChl-b and BPh-b molecules of the L- and M-branches can be rotated on top of each other using a single transformation with the reasonably low r.m.s. deviation of 0.38 Å between the positions of equivalent atoms, a closer inspection shows considerable differences between the local symmetry operations of the special pair, the accessory BChl-b molecules, and the BPh-b molecules. Optimum superposition of the tetrapyrrole rings of the special pair alone is achieved by a rotation of 179.7°, for the accessory BChl-b molecules by a rotation of $-175.8$°, and for the BPh-b molecules by a rotation of $-173.2$°. This deviation from twofold symmetry is illustrated in Figure 12, where the cofactors of the M-branch were rotated using the transformation that optimally superimposes the special pair tetrapyrrole rings. It is clear that, due to the imperfect symmetry, interatomic distances and interplanar angles are different in both branches. For example, the closest distance between the atoms involved in double bonds in the special pair, and in BP$_1$, is shorter by 0.7 Å than the corresponding distance between special pair and BP$_M$. Another example is provided by the angles between the tetrapyrrole rings of the special pair, and those of the accessory BChl-b molecules: the angles for BP$_1$ are about 6° smaller than for BP$_M$. These structural differences lead to differences in overlap of the orbitals, and are expected to lead to different electron transfer properties in the two branches. This may be another contribution to the unidirectional charge separation in the reaction center.

Yet another observation that may relate to the different electronic properties of the L- and M-branches is the different degree of structural order. The amount of disordered structure, measured by the number of atoms without significant electron density, is larger in constituents of the M-branch than in those of the L-branch. Both phytyl side chains of BC$_{M\alpha}$ and BP$_M$ are partially disordered at their ends; the phytyl chains of BC$_{L\alpha}$ and BP$_L$ have a different conformation and are well ordered. The carotenoid near BC$_{M\alpha}$ may contribute to this difference in phytyl chain structure since its presence prevents an identical arrangement of phytyl chains on both sides.

A measure of the rigidity of the structure are the atomic $B$-values obtained during crystallographic refinement. These
values are higher in the M-branch than in the L-branch. An example is the tetrapyrole ring of BP<sub>M</sub> with an average \( B \) value of 21.1 Å<sup>2</sup>; in BP<sub>L</sub>, \( B \) is only 10.3 Å<sup>2</sup>.

A major source of asymmetry are the protein subunits L and M surrounding the core pigments. Their overall sequence homology is only 25%.<sup>1251</sup> Although key residues like the histidines that are ligands to the Mg<sup>2+</sup> ions of the BCHl-b molecules and to the non-heme iron are strictly conserved, most of the residues in contact with the core pigments are different in the two branches.

I will now describe details of the protein environment of the pigments along the pathway of the electron, and mention additional differences between the branches that may be functionally important. Figure 13 shows a close-up view of the structures that are directly involved in the first step of the light-driven electron transfer reaction: the special pair (P), the accessory BCHl-b BCH<sub>LA</sub>, and the first electron acceptor (BP<sub>L</sub>). In addition, a few amino acid residues in close contact with these pigments are shown. BCH<sub>LA</sub> is in van der Waals contact with both the special pair and BP<sub>L</sub>. The closest approach between the tetrapyrole rings of the special pair and BP<sub>L</sub> is 10 Å (atoms in double bonds). The phytol chain of BCH<sub>LP</sub> follows a cleft formed by BCH<sub>LA</sub> and BP<sub>L</sub>; it is in van der Waals contact with both tetrapyrole rings.

At first glance this arrangement suggests that the electron should follow the path P → BCH<sub>LA</sub> → BP<sub>L</sub>. However, attempts to observe bleaching of the absorption bands of BCH<sub>LA</sub> due to transient reduction failed. Spectroscopic experiments with ultrafast laser systems indicated direct reduction of BP<sub>L</sub> from P* without intermediate steps.<sup>145, 46, 50</sup> This result triggered off heated discussions of the mechanism of electron transfer from P to BP<sub>L</sub>, and of the role of BCH<sub>LA</sub> in this process. As indicated in Figure 13 with the example of tyrosine M208, it seems plausible that the protein plays an important role, not only as a scaffold to keep pigments in place, but also in influencing functional properties.

Numerous protein-pigment interactions are apparent also for the special pair itself,<sup>1571</sup> as shown in Figure 14. These interactions include bonds from N<sub>e</sub> atoms of histidines L173 and M200 to the Mg<sup>2+</sup> ions of BCH<sub>LP</sub> and BCH<sub>MP</sub>, respectively. Both acetyl groups of the special pair are hydrogen bonded: BCH<sub>LP</sub> to histidine L168, and BCH<sub>MP</sub> to tyrosine M195. A further hydrogen bond is found between the carbonyl oxygen of ring V and the OH group of threonine L248; there is no equivalent hydrogen bond for BCH<sub>MP</sub>.

The special pair environment is rich in aromatic residues: five phenylalanines, three tyrosines, and three tryptophans are in direct contact with the tetrapyrole rings of the special

Fig. 13. Stereoview of the special pair, BCH<sub>LA</sub>, BP<sub>L</sub>, and selected residues with colored atoms and bonds. Colors as in Fig. 10.

Fig. 14. Stereoview of the special pair and of its protein environment (after Michel et al. [57]): brown, red, residues from the L-subunit; blue, residues from the M-subunit; green, BCH<sub>LP</sub>; yellow, BCH<sub>MP</sub>; hydrogen bonds are indicated in purple. The hydrogen bond between serine M203 and BCH<sub>MP</sub> is no longer present in the refined model.
pair. Tyrosine L162 is located between the special pair and the closest heme group (HE3) of the cytochrome, and may play a role during reduction of the photooxidized special pair (P') by cytochrome [57].

Figure 15 shows BP1, the first electron acceptor, with its protein environment. The BP1 molecules are held in their places by non-covalent interactions only. In the positions where histidine ligands of BCHl-b molecules would be expected, we find leucine M212 in the case of BP1 (see Fig. 15), and methionine L184 in the case of BP1. BP1 forms two hydrogen bonds to the protein. The one between the ester carbonyl group of ring V and tryptophan L100 has an equivalent in a hydrogen bond between BP1 and tryptophan M127. The other hydrogen bond, between the keto-carbonyl oxygen of ring V and glutamic acid L104 is unique for the L-branch; the residue on the M-side corresponding to glutamic acid L104 is valine M131. Glutamic acid L104 is conserved in all currently known sequences of reaction center L-subunits from purple bacteria. Its position in the electron transfer pathway strongly suggests that it is protonated; otherwise, the negative charge of the ionized glutamic acid side chain would make electron transfer to BP1 energetically highly unfavorable.

As for the special pair, aromatic residues are found in the neighborhood of the PBH-b; the neighborhood of BP1 is richer in aromatic residues than that of BP1. An especially noteworthy aromatic residue is tryptophan M250 whose side chain forms a bridge between BP1 and the next electron acceptor, Qa. The M-branch residue equivalent to tryptophan M250 is phenylalanine L216 which, due to the smaller side chain, cannot perform a similar bridging function between BP1 and QA.

The environment of the quinone molecules and of the non-heme iron [57] is shown in Figure 16. Instead of the quinone, however, the figure shows the herbicide terbutryn in the QA binding pocket. The non-heme iron appears in the center of the drawing, between the binding sites of QA and QA, very near the central local twofold symmetry axis. It is bound by five protein side chains, four histidines (L190, L230, M217, M264), and glutamic acid M232, whose carboxylate group acts as a bidentate ligand. The iron sits in a distorted octahedral environment with the axial ligands histidine L230 and histidine M264, and equatorial ligands histidine L190, histidine M217, and glutamic acid M232. Histidine L190 and histidine M217 also contribute significantly to the binding of QA and QA, respectively. The location of the iron and its binding to residues from subunits L and M immediately suggests that a part of the iron's role is to increase the structural stability of the reaction center. It is surprising that its role in electron transfer between the quinones seem to be relatively minor [58].

The head group of QA is bound in a highly hydrophobic pocket; its carboxyl oxygens are hydrogen bonded to the peptide NH groups of alanine M258, and to the Nα atoms of the histidine M217 bound to iron. As mentioned above, tryptophan M250 forms part of the QA's binding pocket; its indole ring is nearly parallel to the head group of QA, at a distance of 3.1 Å. The isoquinoid side chain of QA is folded along the surface of the L-M complex; the last three isoquinoid units are disordered in the crystal. The QA binding pocket is well shielded from the cytoplasm by the globular domain of the H-subunit.

The QA binding site in the crystals of the reaction center is only partially occupied; the QA model is therefore less reliable than the other parts of the structural model discussed above. Nevertheless, the crystallographic data suggest a highly plausible arrangement of the QA head group in its pocket; the QA side chain remains undefined. Apparently QA, similarly to QA, forms hydrogen bonds to the protein with its two carboxyl oxygens: one to the Nα atom of the histidine L190 bound to iron, and a bifurcated hydrogen bond to the OH group of serine L223, and to the NH group of glycine L225. Like tryptophan M250 in the case of QA, phenylalanine L216 forms a significant part of the QA binding pocket. Major differences between the binding sites of QA and QA are the more polar nature of the QA site, and the presence of pathways through the protein, through which protons may enter the QA site. The bottom of the QA site is formed to a large part by the side chain of glutamic acid L212. Protons can move from the cytoplasm along a path marked by charged or polar residues to glutamic acid L212 and from there, by an as yet unknown mechanism, to the doubly reduced QA^-.
al basis for understanding mutations that lead to herbicide-resistant *Rps.-viridis*. The fact that herbicides which were developed to inhibit photosystem II reaction centers of green plants can also inhibit reaction centers of purple bacteria is one of the many indications of a close structural similarity between these kinds of photosynthetic reaction centers (see also Section 4 and Ref. [62]).

4. The Relation to Photosystem II and Evolutionary Aspects

4.1. Conclusions on the Structure of Photosystem II Reaction Center

The most surprising result of the X-ray structure analysis was the discovery of the nearly symmetric arrangement of the reaction center core formed by the homologous L- and M-subunits together with the pigments. The primary electron donor as well as the ferrous non-heme iron (II) are found at the interface between both subunits. Both subunits are needed to establish the reaction center.

Parallel to our X-ray structure analysis the following results suggesting a close relation between the reaction centers from purple bacteria and photosystem II were or became available: i) Photosystem II reaction center and the reaction center from purple bacteria both possess two pheophytin molecules. Upon removal of the quinines or prereduction of them it is possible to trap one electron on one of them. ii) Both reaction centers possess a magnetically coupled $Q_A$–Fe–$Q_b$ complex. iii) The L-subunit of the reaction center of purple bacteria and the D1 protein (which is the product of the psbA-gene and also called $Q_b$ protein, 32 kD-protein or herbicide binding protein) bind the herbicide azidoflavone on photoaffinity labeling. Weak but significant sequence homologies between the L- and M-subunits of the purple bacteria and the D1 proteins and later also D2 proteins of the photosystem II were discovered.

The conclusion to be drawn from the results was obvious: The reaction center of photosystem II from plants and algae had to be expected to be formed by the D1 and D2 proteins with D1 corresponding to the L-subunit and D2 corresponding to the M-subunit. This, however, was at variance with the accepted view that the so-called CP47, a chlorophyll-binding protein with apparent molecular weight of 47000, is the apoprotein of the photosystem II reaction center. Figure 17 compares the amino acid sequences of the L- and M-subunits from two purple bacteria with the D1 and D2 proteins from spinach chloroplasts. Significant sequence homology starts with the glycine-glycine pair (L83, 84, M110,
Several important differences exist between the reaction centers of photosystem II and those of the purple bacteria: the amino acids involved in the binding of the accessory bacteriochlorophylls in the purple bacteria, and a glutamic acid (M232) which is a bidentate ligand to the ferrous non-heme iron are not conserved. There is no indication of the existence of an analogue to the H-subunit in the reaction center of the photosystem II. The overall structure of the photosystem II reaction center core, however, must be very similar to the reaction center from purple bacteria formed by the L- and M-subunits. Figure 18 shows those helices which are presumably conserved between the reaction center cores of the purple bacteria and photosystem II and the position of the amino acids conserved between the L- and M-subunits and the D1 and D2 proteins. The identities of amino acids which are found specifically in the L-subunits and the corresponding positions of the D1 proteins, or specifically in the M-subunits and the corresponding positions of the D2 proteins,
evolutionarily related. A common ancestor possessed an entirely symmetric reaction center with two parallel electron transporting pigment branches across the membrane. This symmetric reaction center was formed by two copies of the same protein subunit encoded by one gene, i.e. was a homodimer. After a gene duplication and subsequent mutations the formation of the asymmetric dimer ("heterodimer") and the use of only one pigment branch for electron transfer became possible. It is an open question whether in evolution this gene duplication occurred only once (before the lineages leading to the purple bacteria and the organisms containing photosystem II split) or twice, after the splitting into these two lineages. In the latter case the specific sequence similarities between L and D1, as well as those between M and D2, would be the result of convergent evolution, whereas the identities of the structurally important amino acids would date back to the original symmetric dimer. Sequence comparisons are in favor of the latter possibility (see Ref. [81]): The similarity of the sequences in the D1 and D2 proteins is much greater than that in the L- and M-subunits. This observation possibly indicates that the gene duplication giving rise to separate D1 and D2 proteins occurred later during evolution than the gene duplication leading to the L- and M-subunits. On the other hand, due to more and stronger interactions with neighboring proteins, the D1 and D2 proteins had less freedom to mutate than the L- and M-subunits. As a result, sequence comparisons might be misleading.

These evolutionary relationships also indicate that there must be an advantage for reaction centers possessing only one active electron transport chain with two quinones acting in series. There might be rather trivial explanations for the use of only one branch, e.g. an asymmetry in the protein environment can cause an asymmetry in the distribution of electrons in the excited state and subsequently lead to a preferred release of an electron only in one direction. This existing polarity might lead to a faster rate of the first electron transfer step, a minimization of competing reactions, and thus a higher quantum yield for the electron transfer.

A clear advantage of the present day's reaction centers is that the two quinones act in series, and only the released secondary quinone, $Q_b$, is a two-electron carrier. Consider the situation of the ancient symmetric reaction center: After the first excitation the electron is transferred to the quinone at the end of one pigment branch. The resulting semiquinone is not stable and its electron is lost within a period of seconds. Only if it receives a second electron can it be protonated and energy stored in the form of the quinol. With two identical parallel electron transfer chains the probability for the second electron to be funneled into the same chain to the same quinone as the first electron is only 50%. A possible electrostatic repulsion by the negatively charged semiquinone might even decrease this probability. In a frequent situation the absorption of two photons leads to the formation of two semiquinones in the same reaction center and energy is not stored in a stable way. Clearly, the way out of this dilemma is to switch the two quinones in series and to allow protonation and release only to the final quinone, which is then $Q_b$ in the electron transfer chain, as is observed in the reaction centers of purple bacteria and photosystem II. A considerable increase in the efficiency of light energy conversion must result, especially under poor light conditions.

4.2. Evolutionary Aspects

The sequence similarities discussed above suggest that the reaction centers from purple bacteria and photosystem II are
5. Aspects of Membrane Protein Structure

5.1. The Membrane Anchor of the Cytochrome Subunit

X-ray structure analyses established that the L and M subunits are firmly integrated into the membrane, both possessing five transmembrane helices, whereas the H subunit is anchored to the membrane by one transmembrane helix. The X-ray work showed no indication of any intramembraneous part of the cytochrome subunit. Nevertheless, in the hands of the biochemists it behaved like a membrane protein and aggregated easily. A strange observation during the protein sequencing was that upon Edman-degradation of the isolated cytochrome subunit no N-terminal amino acid could be identified after the first degradation, but a normal sequence could be obtained starting with the second amino acid from the N-terminus. With the help of F. Lottspeich, K. A. Weyer was then able to isolate a modified amino-terminal amino acid, and, in collaboration with W. Schäfer to elucidate its structure using mass spectrometry.\textsuperscript{146, 182} The result is shown in Figure 19. The N-terminal amino acid is a cysteine linked to a glycerol residue via a thioether bridge. Two fatty acids are then esterified to the two OH-groups of the glycerol. The fatty acids are a statistical mixture of singly unsaturated C\textsubscript{18} fatty acids and singly hydroxylated C\textsubscript{18} fatty acids. These experiments firmly established that the cytochrome subunit also possesses a membrane anchor, but this is now of a lipid type and not of a peptide type. The membrane anchor is very similar to that of the bacterial lipoproteins (see, e.g.,Refs.\textsuperscript{83, 84}). The cytochrome subunit of the reaction center is the first cytochrome molecule known to contain such a membrane anchor.

5.2. Protein Lipid Contacts

The interaction between lipids and protein occurs at the surface of the proteins. Therefore a closer examination of the surface of the protein complex might be very informative. For this purpose a space filling model of the reaction center is shown in Figure 20a. Carbon atoms approaching the surface of the reaction center are shown as white spheres. A central section perpendicular to the approximate twofold rotation axis can be seen where carbon atoms form the surface of the protein almost exclusively. They are mainly side chain atoms of the amino acids leucine, isoleucine and phenylalanine. This central zone must correspond to the hydrophobic part of the protein surface, which in the membrane is in contact with the alkane chains of the lipids. Approaching the cytoplasmic rim of that central zone a row of nitrogen atoms is seen at the protein surface. These nitrogen atoms are side chain atoms of the basic amino acids arginine and histidine. The role of these basic residues might be to determine the position of the reaction center perpendicular to the membrane via specific interaction between negatively charged phosphate groups of the lipids and the positively charged amino acid side chains of the reaction center protein subunits.

Figure 21 shows the percentage of the “accessible surface area” occupied by carbon atoms, as layers perpendicular to the central twofold rotation axis. The twofold rotation axis runs through the non-heme iron atom near the cytoplasmic side and relates the special-pair bacteriochlorophyll molecules near the periplasmic side of the membrane. Two important conclusions can be drawn from Figure 21: (i) The primary electron donor (special pair), is located in the hydrophobic non-polar part of the membrane, whereas the non-heme iron atom is already in that zone where the protein surface is polar and most likely interacts with the polar head groups of the lipids. (ii) The thickness of the hydrophobic zone perpendicular to the membrane is 30 to 31 Å only. This value is smaller than expected for a lipid bilayer composed of lipids with C\textsubscript{18} fatty acids.

5.3. Distribution of Amino Acids

Bound Water Molecules

Figure 20b shows the distribution of the strongly basic amino acids arginine and lysine, and of the strongly acidic amino acids glutamic acid and aspartic acid, which at neutral pH possess electric charges at the ends of their side chains. A central zone, where none of these amino acids is found, has a thickness of about 25 Å and is thus slightly thinner than the hydrophobic surface zone shown in Figures 20 and 21. This slight discrepancy is due to two arginine residues and one glutamic acid residue, which are apparently in a hydrophobic environment without counter charges. The role of the positive charges of the arginine side chains seems to be structural. They possibly cancel the partial negative charge at the carboxy-terminal ends of the short helices in the connections of the long D and E transmembrane helices. These short de helices partly intrude into the hydrophobic zone of the membrane and a positive charge seems to be necessary so that the peptide chain can change its direction. The glutamic acid (L104) seems to be protonated and thus neutral, and forms a hydrogen bond with one of the bacteriopheophytin molecules (BP\textsubscript{1})\textsuperscript{157} (see also Section 3.5).

Within the L and M subunits the glutamate and aspartate, as well as lysine and arginine residues show an interesting asymmetric distribution with respect to cytoplasmic and periplasmic sides. If one calculates “net charges” for the
Fig. 20. a) Space-filling model of the photosynthetic reaction center of Rps. viridis. Carbon atoms are shown in white, nitrogen atoms in blue, oxygen atoms in red, and sulfur atoms in yellow. The atoms of a bacteriopheophytin molecule visible on the surface are represented in brown. b) Distribution of the “charged” amino acids in the photosynthetic reaction center of Rps. viridis. The negatively charged amino acids (aspartic, glutamic) are shown in red, the positively charged amino acids (arginine, lysine) in blue. c) Distribution of tryptophan residues (green) in the L- (brownish) and M-subunits (blue). d) Distribution of bound water molecules in the reaction center. The reaction centers and the L- and M-subunits are always viewed parallel to the membrane.

Fig. 21. Percentage of the accessible surface area (ACSA) occupied by carbon atoms, shown for 3 Å-thick layers perpendicular to the noncrystalllographic twofold rotation axis, which runs through the ferrous non-heme iron atom (Fe) and the special pair (SpP).

peptide chains on the periplasmic side of the membrane and compares them with the net charges of the cytoplasmic side (assuming that all glutamic acid residues, aspartic acid residues and the carboxy-termini are negatively charged, whereas all the arginine and lysine residues and the amino-termini are positively charged) one finds that the cytoplasmic ends of the transmembrane helices and their respective connections are nearly always less negatively charged than their counterparts on the periplasmic side. This phenomenon is illustrated schematically in Figure 22. As a result the cytoplasmic part of the M-subunit carries four positive net charges and the periplasmic part four negative charges, the cytoplasmic part of the L-subunit two positive charges and the periplasmic part four negative charges. The charge asymmetry becomes even more pronounced if one considers the existence of the firmly bound non-heme iron atom on the cytoplasmic side and the presumed protonation of glutamic acid L104. Thus, these membrane proteins are strong electric dipoles. This result can be correlated with the fact that the interior of bacteria is negatively charged, due to the action of electrogenic ion pumps. This means that the L- and M-subunits are oriented in the membrane in the energetically more favorable manner. Conversely, the combination of the electric field across the membrane, established by the ion pumps, and the anisotropic distribution of negatively and positively charged amino acids in the protein may be one of the factors which determine the orientation of membrane proteins with respect to the inside and outside of the cell.
peptide oxygen atoms. Another hydrogen bond with an asparagine side chain is possible. Just how much these water molecules contribute to the stability of the structure of the reaction center has still to be clarified.

5.4. Crystal Packing and Detergent Binding

As outlined in Section 1, the most promising strategy was to crystallize the reaction center within a detergent micelle. According to this concept the crystal lattice should be formed by polar interactions between polar surface domains of the reaction center. This expectation was confirmed by the results of the structural analysis. Mainly the polar surfaces of the cytochrome subunit and the H-subunit are involved in the crystal packing, and only to a minor extent the polar surface part of the M-subunit.

As expected for detergents in a micelle most of the detergent is crystallographically not ordered and, with one exception, cannot be seen in the electron density map. The single transmembrane helix of the H-subunit, two transmembrane helices of the M-subunit, and part of the pigments seem to form a pocket in which one detergent molecule is bound. Its polar head-group apparently undergoes specific interactions with the protein near the cytoplasmic end of the hydrophobic surface zone. Specific binding of this particular detergent molecule might explain why crystals of the photosynthetic reaction center from Rhodopseudomonas viridis could be grown only with N,N-dimethyldecylamine-N-oxide as detergent, but not when octyl glucopyranoside or similar detergents were used.

In collaboration with M. Roth and A. Bentley-Lewit from the Institut Laue-Langevin in Grenoble the detergent micelle could be made visible by neutron crystallography and H$_2$O/D$_2$O contrast variation. A rather flat, monolayer-like ring of detergent molecules surrounding the hydrophobic surface zone of the reaction center became visible. Regions where the detergent micelles are in contact can also be seen. Therefore, attractive interactions between detergent micelles may also contribute to the stability of the protein’s crystal lattice. In general, the strategy to crystallize membrane proteins within their detergent micelles[16, 46] now seems to be successful; however, the progress made in crystallizing other membrane proteins has been unexpectedly slow. Well diffacting crystals have only been obtained in the case of bacterial photosynthetic reaction centers and bacterial porins. The necessary fine tuning with respect to the size of the detergent micelle and the size of the polar head group of the detergent is still a formidable task which has to be solved empirically for each individual membrane protein.

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General hydrogenations

Ryoji Noyori realized the need for more selective catalysts with broader applications. Among the catalysts he has developed is the Rh-BINAP system, which is used for the synthesis of (S)-1,2-propanediol in the production of an antibiotic, levofloxacin. Noyori's catalysts are widely used for the synthesis of fine chemicals and pharmaceutical products as well as new advanced materials.
1. Prologue

Chirality (handedness; left or right) is an intrinsic universal feature of various levels of matter.[1] Molecular chirality plays a key role in science and technology. In particular, life depends on molecular chirality, in that many biological functions are inherently dissymmetric. Most physiological phenomena arise from highly precise molecular interactions, in which chiral host molecules recognize two enantiomeric guest molecules in different ways. There are numerous examples of enantiomer effects which are frequently dramatic. Enantiomers often smell and taste different. The structural difference between enantiomers can be serious with respect to the actions of synthetic drugs. Chiral receptor sites in the human body interact only with drug molecules having the proper absolute configuration, which results in marked differences in the pharmacological activities of enantiomers. A compelling example of the relationship between pharmacological activity and molecular chirality was provided by the tragic administration of thalidomide to pregnant women in the 1960s. (R)-Thalidomide has desirable sedative properties, while its S enantiomer is teratogenic and induces fetal malformations.[2, 3] Such problems arising from inappropriate molecular recognition should be avoided at all costs. Nevertheless, even in the early 1990s, about 90% of synthetic chiral drugs were still racemic—that is, equimolar mixtures of both enantiomers, which reflects the difficulty in the practical synthesis of single-enantiomeric compounds.[4] In 1992, the Food and Drug Administration in the U.S. introduced a guideline regarding “racemic switches”, in order to encourage the commercialization of clinical drugs consisting of single enantiomers.[5] Such marketing regulations for synthetic drugs, coupled with recent progress in stereoselective organic synthesis, resulted in a significant increase in the proportion of single-enantiomer drugs. In 2000, the worldwide sales of single-enantiomer compounds reached 123 billion U.S. dollars.[6] Thus, gaining access to enantiomerically pure compounds in the development of pharmaceuticals, agrochemicals, and flavors is a very significant endeavor.

Discovery of truly efficient methods to achieve this has been a substantial challenge for chemists in both academia and industry. Earlier, enantiomerically pure compounds were obtained by the classical resolution of a racemate or transformation of readily accessible, naturally occurring chiral compounds such as amino acids, tartaric and lactic acids, carbohydrates, terpenes, or alkaloids. Even though stereoselective conversion of a prochiral compound to a chiral product, namely through an asymmetric reaction, is the most attractive approach, practical access to pure enantiomers relied largely on biochemical or biological methods. However,

Asymmetric Catalysis: Science and Opportunities (Nobel Lecture) **

Ryoji Noyori*

Asymmetric catalysis, in its infancy in the 1960s, has dramatically changed the procedures of chemical synthesis, and resulted in an impressive progression to a level that technically approximates or sometimes even exceeds that of natural biological processes. The recent exceptional advances in this area attest to a range of conceptual breakthroughs in chemical sciences in general, and to the practical benefits of organic synthesis, not only in laboratories but also in industry. The growth of this core technology has given rise to enormous economic potential in the manufacture of pharmaceuticals, animal health products, agrochemicals, fungicides, pheromones, flavors, and fragrances. Practical asymmetric catalysis is of growing importance to a sustainable modern society, in which environmental protection is of increasing concern. This subject is an essential component of molecular science and technology in the 21st century. Most importantly, recent progress has spurred various interdisciplinary research efforts directed toward the creation of molecularly engineered novel functions. The origin and progress of my research in this field are discussed.

Keywords: asymmetric catalysis • asymmetric hydrogenation • Nobel lecture • Pligands • ruthenium

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Asymmetric Catalysis

the scope of such methods using enzymes, cell cultures, or whole microorganisms is limited because of the inherent single-handed, lock-and-key specificity of biocatalysts. On the other hand, a chemical approach allows for the flexible synthesis of a wide array of enantiopure organic substances from achiral precursors. The requirements for practical asymmetric synthesis include high stereoselectivity, high rate and productivity, atom economy, cost efficiency, operational simplicity, environmental friendliness, and low-energy consumption. Traditional asymmetric synthesis using a stoichiometric amount of a chiral compound, though convenient for small to medium-scale reactions, is practical only if the expensive chiral auxiliary deliberately attached to a substrate or reagent is readily recyclable; otherwise it is a wasteful procedure.

Figure 1 illustrates a general principle of asymmetric catalysis which provides an ideal way for multiplying molecular chirality. A small amount of a well-designed chiral catalyst can combine A and B, which produces the chiral AB compound stereoselectively in a large quantity. Of various possibilities, the use of chiral organometallic molecular catalysts would be the most powerful strategy for this purpose. Asymmetric catalysis is an integrated chemical approach in which the maximum chiral efficiency can be obtained only by a combination of suitable molecular design with proper reaction conditions. The reaction must proceed with a high turnover number (TON) and a high turnover frequency (TOF), while the enantioselectivity ranges from 50:50 (nonselective) to 100:0 (perfectly selective). The chiral ligands that modify intrinsically achiral metal atoms must possess suitable three-dimensional structures and functionality, to generate sufficient reactivity and the desired stereoselectivity. Sometimes the properties of achiral ligands are also important. The chiral catalyst can permit kinetically precise discrimination among enantiotopic atoms, groups, or faces in achiral molecules. Similarly, enantiomeric molecules can also be discriminated. Certain well-designed chiral metal catalysts not only accelerate the chemical reactions repeatedly but also differentiate between diastereomeric transition states (TSs) with an accuracy of 10 kJ mol⁻¹. In this way, such compact molecular catalysts with a molecular weight less than 1000, or <20 Å in length or diameter, allow for an ideal method for synthesizing enantiomeric compounds. The diverse catalytic activities of metallic species, as well as the virtually unlimited structural variation of the organic ligand, provides enormous opportunities for asymmetric catalysis.

2. Discovery of Asymmetric Catalysis by Chiral Organometallic Complexes

In 1966, when I was in H. Nozaki’s (Figure 2) laboratory at Kyoto, we discovered the first example of asymmetric catalysis using a structurally well-defined chiral transition-metal complex. This finding resulted from research done for an entirely different purpose, which was to elucidate the mechanism of carbone reactions. As illustrated in Scheme 1, when a small amount (1 mol%) of a chiral Schiff base – Cu⁴⁺ complex was used as a molecular catalyst in the reaction of styrene and ethyl diazoacetate, the cis- and trans-cyclopropanecarboxylates were obtained in 10 and 6% enantiomeric excess (ee), respectively. We also observed asymmetric induction in carbone insertion to a C–O bond of 2-phenyl-oxetane, which gave optically active 2,3-substituted tetrahydrofuran derivatives. At that time, the finding was syntheti-
Scheme 1. Discovery of asymmetric reaction by means of a chiral organometallic molecular catalyst.

3. Asymmetric Hydrogenation in the Early Days

At present the asymmetric cyclopropanation is important practically, but in the late 1960s, it was just a special reaction in organic synthesis. I decided to pursue hydrogenation, which is a core technology in chemistry. It is the simplest but most powerful way to produce a wide array of important compounds in large quantities using inexpensive, clean hydrogen gas without forming any waste. Hydrogenation was initiated at the end of the 19th century by P. Sabatier (1912 Nobel laureate), who used fine metal particles as heterogeneous catalysts. Some notable achievements that attracted me, before doing research in this area, include: activation of H₂ by a transition-metal complex in the late 1930s (M. Calvin, 1961 Nobel laureate), homogeneous hydrogenation of olefinic substrates with RuCl₃ in 1961 (J. Halpern, J. Harrod, and B. R. James), and hydrogenation of olefinic compounds using [RhCl(P(C₆H₅)₃)₂] in 1965 (G. Wilkinson, 1973 Nobel laureate). Most importantly, in 1956, S. Akabori at Osaka reported that metallic Pd drawn on silk catalyzes asymmetric (heterogeneous) hydrogenation of oximes and oxazolones. This pioneering work, though not effective synthetically, was already well known throughout Japan. In 1968, two years after our asymmetric cyclopropanation in 1966, W. S. Knowles (fellow Nobel laureate in 2001) and L. Horner independently reported the first homogeneously catalyzed asymmetric hydrogenation of olefins with chiral monodentate tertiary phosphane–Rh complexes, albeit in 3–15% optical yield. H. B. Kagan provided a major breakthrough in this area in 1971, when he devised DIOP, a C₂-chiral diphosphane ligand derived from tartaric acid. He used its Rh complex for asymmetric hydrogenation of dehydro amino acids leading to phenylalanine in about 80% ee, then recorded as 72% ee. The Knowles group at Monsanto established a method for the industrial synthesis of l-DOPA, a drug for treating Parkinson’s disease, which used his DIPAMP–Rh catalyzed asymmetric hydrogenation as a key step. These achievements significantly stimulated the subsequent investigation of this important subject.

Shortly after moving from Kyoto to Nagoya in 1969–70, I spent a postdoctoral year at Harvard with E. J. Corey (1990 Nobel laureate). He asked me to hydrogenate selectively one of the two C=O bonds in a prostaglandin F₂α derivative to give the F₂α form having only one C=O bond. This research was helped by K. B. Sharpless (another fellow Nobel laureate in 2001), who was then a postdoctoral fellow with K. Bloch (1964 Nobel laureate in Physiology or Medicine) and who suggested a convenient TLC technique for analyzing the structurally very similar olefinic compounds. In addition to this background, my personal interaction with J. A. Osborn, a former Wilkinson student and co-inventor of [RhCl(P(C₆H₅)₃)₂] who was then an Assistant Professor at Harvard, greatly enhanced my interest in asymmetric hydrogenation, which later became my life-long research interest. My desire was to develop a truly efficient asymmetric hydrogenation which would have a wide scope of applications. In the early 1970s, chiral phosphane–Rh complexes could hydrogenate satisfactorily only dehydro amino acids but not many other olefins. Asymmetric hydrogenation of ketones was totally unexplored.
4. BINAP, a Beautiful Chiral Molecule

H$_2$ is the simplest molecule but it has enormous potential from both a scientific and technical point of view. To discover high-performance asymmetric catalysts, the development of an excellent chiral ligand is crucial. Attracted by its molecular beauty,[23] we initiated the synthesis of BINAP (2,2'-bis(diphenylphosphinoyl)-1,1'-binaphthyl)[23] in 1974 at Nagoya with the help of H. Takaya, my respected long-term collaborator. BINAP was a new, fully aromatic, axially dissymmetric C$_2$-chiral diphosphane that would exert strong steric and electronic influences on transition-metal complexes. Its properties could be fine-tuned by substitutions on the aromatic rings. However, synthesis of this optically pure C$_2$-chiral diphosphane was unexpectedly difficult. In 1976, for the first time, we managed to obtain optically active BINAP starting from optically pure 2,2'-diamino-1,1'-binaphthyl (Scheme 2a). However, this seemingly straightforward synthetic pathway was not reproducible, because of the tendency of the chiral intermediates to cause racemization.[25] In 1978, we found a reliable method for resolving racemic BINAP with an optically active dimethyl(1-phenylethyl)aminopalladium(II) chloride complex,[23] while, later, optically pure BINAP became available more conveniently by resolution of BINAP dioxide with camphorsulfonic acid or 2,3-O-dibenzoyltartaric acid (Scheme 2b).[24, 25]

Although the elusive BINAP was available, our goal was still in the distance. Enantioselectivity of BINAP–Rh catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids was highly variable and not satisfactory at that time, ee values of the chiral products being at most about 80%. However, we remained patient. In 1980, six years after the start, thanks to the unwavering efforts of my young associates, we published our first work on asymmetric synthesis of amino acids of high enantiomeric purity, up to 100% ee, together with the X-ray crystalline structure of a cationic BINAP–Rh(norbornadiene) complex.[22, 26]

BINAP, a conformationally flexible atropisomeric C$_2$ diphosphane, can accommodate a range of transition metals by rotating about the binaphthyl C(1)-C(1') pivot and C(2 or 2')-P bonds, without seriously increasing torsional strain, while the resulting seven-membered chelate rings containing only sp$^3$ carbon atoms are in turn skeletaly unambiguous. The chirality of BINAP is transmitted to other metal-coordination sites through the chelate structure.[22, 26] The δ or λ geometry is highly skewed and determines the chiral disposition of the P-phenyl rings that play a key role in generating outstanding chirality-discriminating ability at the reactive coordination sites. Thus BINAP-based metal complexes were expected to exhibit high chiral-recognition ability in various catalytic reactions, in addition to hydrogenation.

5. Asymmetric Synthesis of Menthol

The cationic BINAP–Rh complex was best used in asymmetric isomerization of allylic amines,[27] which realized an industrial synthesis of (-)-menthol from myrcene (Scheme 3).[28] This resulted from a fruitful academic/industrial collaboration between groups at Osaka University (S. Otsuka and H. Tanii),[29] Nagoya University (R. Noyori), Institute for Molecular Science (H. Takaya), Sizuoka University (J. Tanaka and K. Takabe),[30] and Takasago International Co. (Figure 4). The key step was the asymmetric isomerization of geranyl(allylic)amine, catalyzed by an (S)-BINAP–Rh complex in THF and forming (R)-citronellal enamine, which upon hydrolysis gives (R)-citronellal in 96–99% ee. This is far superior to the 80% ee of the naturally occurring product available from rose oil. Among various Rh and other catalysts examined, the BINAP-based cationic Rh complex was the most reactive and the most stereoselective. The BINAP–Rh catalyst clearly differentiates between the pro-S and pro-R hydrogen atoms on the flexible allylic amine skeleton during the 1,3-suprafacial shift that occurs by a nitrogen-triggered mechanism.[31] The asymmetric reaction is performed on a nine-ton scale. The full technical refinements of the position- and stereo-
selective addition of diethylamine to myrcene, which gives the starting geranylamine, and the ZnBr₂-catalyzed intramolecular ene reaction of \((R)\)-citronellal, which forms isopulegol with the three correct stereogenic centers, allowed for the production of terpenic substrates totaling about 1500 tons per year at Takasago International Co. Most of the \((R)\)-citronellal is converted to 1000 tons per year of \((-)\)-menthol, one-third of the world demand. \((R)\)-7-Hydroxydihydrocitronellal thus prepared is a perfumery agent that smells like lily of the valley. Its methyl ether is an intermediate in the synthesis of methoprene, a growth regulator of the yellow-fever mosquito.\(^{[22, 23]}\)

Figure 4. At the Takasago plant for \((-)\)-menthol synthesis (February, 1984). From the left, K. Tani, H. Takaya, R. Noyori, S. Otsuka, S. Akutagawa, and H. Kumobayashi.

6. Asymmetric Hydrogenation of Olefins by BINAP – Ruthenium Complexes

Returning to the topic of asymmetric hydrogenation, our success resulted from the invention of the BINAP ligand\(^{[25]}\) and also from the use of Ru, which behaves differently from the conventional Rh.\(^{[33, 34]}\) The cationic BINAP – Rh complexes catalyze hydrogenation of \(\alpha\)-(acylamino)acrylic acids or esters to give the corresponding amino acid derivatives in high ee values (Scheme 4).\(^{[22, 23]}\) However, the reaction is relatively slow, and high enantioselectivity is obtained only under special conditions, probably because of the operation of the unsaturate/dihydride mechanism. J. Halpern\(^{[35]}\) and J. M. Brown\(^{[36]}\) showed that hydrogenation of enamides in the presence of a \(C_2\)-chiral diphosphane – Rh complex proceeds by oxidative addition of \(H_2\) to diastereomeric Rh – substrate chelate complexes, followed by stepwise transfer of the two hydrides to the coordinated olefin. Most significantly, the minor diastereomer of these complexes is the more reactive one.\(^{[37]}\) Because of the excellent chiral-recognition ability of BINAP, the reactive species, which leads to the desired hydrogenation product, is present in a very small quantity and is even NMR-invisible in the equilibrium mixture.\(^{[38]}\) Therefore, conditions such as hydrogen pressure, temperature, and concentration must be chosen carefully to obtain high enantioselectivity. Furthermore, asymmetric hydrogenation was limited to the synthesis of amino acids.

A major breakthrough occurred when we devised the BINAP – Ru\(^{II}\) dicarboxylate complexes in 1986 (Figure 5).\(^{[38, 39]}\) The Ru complexes are excellent catalysts for asymmetric hydrogenation of various functionalized olefins, as summarized in Scheme 5. The reaction proceeds via a Ru monohydride intermediate formed by heterolysis of \(H_2\) by the Ru complex. The Ru center remains in the \(+2\) oxidation state throughout the catalytic cycle in contrast to the Rh complex, which involves a \(+1\)/\(+3\) redox process. Heteroatoms in the functional groups serve as a binding tether to the catalytic Ru center. This hydrogenation has a very wide scope. Hydrogenation of \(\alpha,\beta\)- and \(\beta,\gamma\)-unsaturated carboxylic acids takes place in alcoholic media, where the sense and degree of
Asymmetric Catalysis

Figure 5. Structures of BINAP–Ru diacate complexes.

Scheme 5. Asymmetric hydrogenation of functionalized olefins catalyzed by (S)-BINAP–Ru dicarboxylates.

the enantioselection are highly dependent on the substitution pattern and hydrogen pressure.[61] Allylic and homoallylic alcohols are also hydrogenated with high enantioselection.[62] Certain racemic allylic alcohols can be resolved by the BINAP–Ru-catalyzed hydrogenation.[63] The chiral Ru complexes effect highly enantioselective hydrogenation of (Z)-2-acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinolines.[68, 44] In a similar manner, enantio-enriched α- and β-amino acids[65] as well as α-amino phosphonic acids[66] are obtainable from suitably amido-substituted olefins. Notably, the RuII and RhI complexes possessing the same BINAP chirality form anti-podal amino acids as the predominant products.[67]

Scheme 6 illustrates some chiral compounds that can be obtained by this asymmetric hydrogenation. An important application is the synthesis of the anti-inflammatory drug, naproxen, in 97% ee from an α-aryl-acrylic acid.[41, 46] Natural and unnatural citronellol with up to 99% ee are obtainable from geraniol or nerol without saturation of the C(6)–C(7) double bond, with a high substrate to catalyst (S:C) ratio. The hydrogenation of \( (R,E)-6,7,10,11 \)-tetrahydrofarnesol produces \( 3R,7R \)-hexahydrofarnesol, a C15 side-chain of \( \alpha \)-tocopherol (vitamin E) and a part of vitamin K1. The hydrogenation of an allylic alcohol possessing a chiral azetidinone unit gives a \( 1\beta \)-methylcarbapenem synthetic intermediate diastereoselectively.[48] The discovery of this asymmetric hydrogenation made possible the general asymmetric synthesis of isoquinoline alkaloids including morphine, benzomorphans, and morphinans such as the antitussive dextromethorphan.[43, 49]

Importantly, the list of substrates can be extended to include various ketones, as generalized in Scheme 7 and Figure 6. The halogen-containing BINAP–RuII complexes (oligomers),[50] but not the diacate complexes, are efficient catalysts for the asymmetric hydrogenation of a range of functionalized ketones, wherein coordinative nitrogen, oxygen, and halogen atoms near C=O functions direct the

Scheme 6. Applications of BINAP–Ru catalyzed hydrogenation of olefins.
Scheme 7. Asymmetric hydrogenation of functionalized ketones catalyzed by (S)-BINAP–Ru dihalide complexes (X = halogen).

Figure 6. H. Takaya, M. Kitamura, and T. Ohkuma (from the left) made major contributions to the asymmetric hydrogenation of functionalized ketones catalyzed by (S)-BINAP–Ru dihalide complexes.

reactivity and stereochemical outcome in an absolute sense.[55] A wide variety of achiral ketones are hydrogenated enantioselectively to the corresponding chiral alcohols in 90–100% ee, in a predictable manner. The reaction can normally be performed in alcohols with up to 50% substrate concentration under 4–100 atm at room temperature with an S:C ratio of up to 10000:1 on any scale, even using >100 kg of the substrate. Scheme 8 shows some synthetic applications of this asymmetric hydrogenation. (R)-1,2-Propanediol thus obtained from hydroxyacetone is used for industrial synthesis of the antibacterial levofloxacin (Takasago Co./Daichi Pharmaceutical Co.). In addition, γ-amino-β-hydroxybutyric acid (GABOB) and a compactin intermediate can be prepared with high enantiomeric purity,[49, 52] Pre-existing stereogenic centers in the ketonic substrate significantly affect the steric course. Statines can be obtained with a high diastereo- and enantioselectivity.[53] The double hydrogenation of 1,3-diones via chiral hydroxy ketones leads to the anti 1,3-diols in close to 100% ee.[51a]

Racemic β-keto esters with a configurationally labile α-stereogenic center, by undergoing in situ stereoinversion, can be transformed into a single stereoisomer out of the four stereoisomers, with high stereoselectivity, as illustrated in Scheme 9.[56] This dynamic kinetic resolution[55] has been used for the synthesis of various biologically important compounds such as threonine, (2S,3R)-3-(3,4-dihydroxyphenyl)serine (l-DOPS),[52] phosphothreonine,[56] and fosfomycin.[57] Its utility was highlighted by the industrial synthesis of carbapenem antibiotics at Takasago International Co. (Scheme 10). The requisite chiral 4-acetoxyazetidinone is prepared by the (R)-BINAP–Ru-catalyzed hydrogenation of racemic methyl α-(benzamidomethyl)acetoacetate in dichloromethane, to give the 2S,3R hydroxy ester with 94:6 erythro/threo diastereoselectivity[58] and 99.5:0.5 enantioselectivity.[54] Quantitative analysis[54] indicates that the 2R substrate is hydrogenated 15 times faster than the R enantiomer, and the slow-reacting R isomer is inverted to the 2S enantiomer 92 times easier than


Scheme 9. Asymmetric hydrogenation by dynamic kinetic resolution. X = Cl, Br.
it is hydrogenated. The extent of the BINAP catalyst-based asymmetric induction is calculated to be 104:1 in favor of the 3R isomer, whereas the substrate-based asymmetric induction is 9:1 in favor of the C(2)/C(3) erythro stereochemistry. The volume of the hydrogenation reactor shown in Figure 7 is 13 m³.

β-Keto esters are the best substrates for the Ru catalyzed asymmetric hydrogenation and lead to the β-hydroxy esters in >98% ee. Figure 8 illustrates the mechanistic model. The halide ligand in the Ru complex, which generates a strong acid and a RuHCl species by the action of H₂, is important to facilitate the hydride transfer from the Ru center to the carbonyl carbon. In addition, the presence of the ester moiety interacting with the Ru center is crucial for both high reactivity and enantioselectivity. Because of the excellent chiral recognition ability of BINAP, the two stereo-determining diastereomeric transition states (TSs) are well differentiated with the assistance of the oxygen–Ru interaction. The R-directing TS is highly favored over the S-generating diastereomer, which suffers from substantial R/P-phenyl repulsive interaction. The oxygen–Ru dative bond (and related interaction in the reactions in Scheme 7) exerts a pivotal function in the acceleration of hydrogenation as well. Thus, β-keto esters are hydrogenated smoothly even in the simplest ketone, acetone, containing a small amount of water. Thus, although BINAP–Ru dihalide catalysts have a very wide scope, they are unable to hydrogenate simple, unfunctionalized ketones.

7. Asymmetric Hydrogenation of Simple Ketones by BINAP/Diamine–Ruthenium Complexes

For more than half a century, selective reduction of simple ketones relied heavily on the metal-hydride chemistry devel-
oped largely by H. C. Brown (1979 Nobel laureate). Chemo-
selective reduction of a C\(=\)O function in the presence of a
C\(=\)C group has been best effected by the stoichiometric
NaBH\(\text{4}\) reagent.\(^{[60]}\) Diastereoselective reduction of ketones
has frequently been achieved by Selectridex.\(^{[61]}\) Enantiosele-
ctive reduction of achiral ketones is effected by chiral
stoichiometric reagents including BINAL-H,\(^{[62]}\) DIP chlor-
ide,\(^{[63]}\) and Alpine-borane\(^{[64]}\), or by the Corey–Bakshi–Shi-
bata (CBS) method combining \(\text{B}_2\text{H}_6\) or catecholborane and a
chiral oxazaborolidine catalyst.\(^{[65]}\) Until very recently, these
types of selective C\(=\)O reductions were not generally achiev-
able by catalytic hydrogenation.\(^{[49d, 66]}\)

In 1995, when I was the director of the ERATO Molecular
Catalysis Project, we found that hydrogenation catalyzed by a
\([\text{RuCl}_2(\text{phosphane})_2\text{(diamine)}]\) complex and an alkaline base
provided a general solution to this long-standing problem.\(^{[67]}\) The
use of appropriate chiral diphosphanes and chiral
diamines allows asymmetric hydrogenation of simple ketones
which lack any Lewis basic functionality capable of interact-
ing with the metal center. The reactivity and stereoselectivity
are fine-tuned by changing the steric (bulkiness and chirality)
and electronic properties of the auxiliaries. As generalized in
Scheme 11, the newly devised BINAP/diamine complex
catalyzes rapid, productive, and highly enantioselective hy-
drogenation of a range of aromatic, heteroaromatic, and
olefinic ketones in 2-propanol containing \(\text{tBuOK or KOH}\).\(^{[68]-[70]}\) Among various complexes, \([\text{RuCl}_2(\text{xylbinap})-\text{(dai-
pen)}]\)\(^{[71]}\) is particularly effective. For example, acetophe-
none and its derivatives are hydrogenated with S:C of up to
100000:1, to give the secondary alcohols quantitatively in
99% \(ee\).\(^{[72]}\) although the diamine-free BINAP–Ru complexes
are totally ineffective. Normally, C\(=\)C bonds are much more
reactive than C\(=\)O in catalytic hydrogenation, but this system
allows for the preferential saturation of a C\(=\)O function over a
coeexisting C\(=\)C linkage.\(^{[73, 74]}\) Olefinic ketones, either conju-
gated or nonconjugated, can be converted to olefinic alcohols
selectively. The hydrogenation tolerates various functionali-
ties including F, Cl, Br, I, CF\(_3\), OCH\(_3\), OCH\(_2\)CH\(_3\), COOCH(CH\(_2\))\(_2\), NO\(_2\), NH\(_2\), and NRCOR. Both electron-
rich (furan, thiophene, thiazole, etc.) and -deficient rings
(pyridine and pyrimidine) are left intact.\(^{[75]}\) The simple
\([\text{RuCl}_2(P\text{Ar}_3)(\text{NH}_2\text{CH}_2\text{CHNH}_2)]\) complex hydrogenates
various substituted cyclic and acyclic ketones with high
diastereoselectivity, where the RuH intermediate acts as a
bulky hydride species.\(^{[76]}\) Because of the basic and protic
nature of the reaction environment, hydrogenation of config-
urationally labile ketones allows for the dynamic kinetic
discrimination of diastereomers, epimers, and enantiom-
ers.\(^{[77]-[79]}\) which effects a new type of stereoselective reductions
of ketones which are not possible with stoichiometric hydride
reagents.

This asymmetric hydrogenation shows promise for the
practical synthesis of a wide variety of chiral alcohols. The
chiral diphosphane/diamine–Ru complexes effect enantiosele-
cctive hydrogenation of certain amino or amido ketones by a
nonchelate mechanism, without interaction between the Ru
center and nitrogen or oxygen atoms.\(^{[70]}\) This method has been
applied to the asymmetric synthesis of various important
pharmaceuticals, which includes (\(R\))-denopamine, a \(\beta\)-recep-
tor agonist, the antidepressant (\(R\))-fluoxetine, the antipsy-
chotic BMS 181100, and (\(S\))-duloxetine, which is a potent
inhibitor of serotonin and norepinephrine uptake carriers
(Scheme 12). Benzophenones can be hydrogenated to benzy-
drils with an S:C ratio of up to 20000:1 without over-
reduction.\(^{[79]}\) Enantioselective hydrogenation of certain ortho-
substituted benzophenones leads to the unsymmetrically
substituted benzhydrols with high \(ee\) values, which allows
convenient synthesis of the anticholinergic and antihistaminic
(\(S\))-orphenadrine. The antihistaminic (\(R\))-neobenodine can
be synthesized by using asymmetric hydrogenation of o-
bromo-\(p\)-methylbenzophenone.

This approach is the first example of general and efficient
asymmetric hydrogenation of \(\alpha\),\(\beta\)-unsaturated ketones to
chiral allylic alcohols of high enantiomeric purity.\(^{[72]-[74]}\) The
selectivity profile is in sharp contrast to that observed with the
diamine-free BINAP–Ru complex, and efficiently catalyzes
asymmetric hydrogenation of allylic alcohols (Scheme 5). Its
utility has been demonstrated by the synthesis of intermedi-
ates of an \(\alpha\)-tocopherol side-chain and arachycyclanes, as well
as \(\beta\)-ionol (Scheme 12).\(^{[72, 74]}\) The asymmetric hydrogenation
shown in Scheme 11 is generally achieved by the combined
use of an (\(S\))-BINAP ligand and an (\(S\))-1,2-diamine (or both
\(R\) enantiomers). This is also the case for the reaction of
\(s\)-cis exocyclic enones, such as (\(R\))-pulegone. However, asym-
metric hydrogenation of 2,4,4-trimethyl-2-cyclohexenone was
affected best with \([\text{RuCl}_2(S\text{-tolbinap})][[(\text{R},\text{R})\text{-dpen}]]\).\(^{[74, 40]}\)
The cyclic allyl alcohol obtained in 96% \(ee\) (Scheme 12) can
be converted into a series of carotenoid-derived odorants and
bioactive terpenes, such as \(\alpha\)-damascone. The \(R\) or \(S\) alcohols
with \(ee\) values as high as 95% can be obtained, even with a

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**Scheme 11.** General asymmetric hydrogenation of simple ketones. \(\text{Ar} = \text{aryl, Het = heteroaryl, Un = alkenyl.} \)
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Scheme 12. Application of asymmetric hydrogenation of simple ketones.

racemic TolBINAP – RuCl₃ complex in the presence of (R,R)- or (S,S)-DPEN by asymmetric activation. In this case, the highly enantioselective hydrogenation catalyzed by the S di-phosphane/R,R diamine complex (or R/S,S combination) turns over 121 times faster than the less stereoselective reaction promoted by the diastereomeric S/S,S (or R/R,R) complex.

The reaction is rapid and highly productive. For example, when a mixture of acetophenone (601 g), the (S)-TolBINAP/ (S,S)-DPEN Ru complex (2.2 mg), and tBuOK (5.6 g) in 2-propanol (1.5 L; 30% w/v substrate concentration) was stirred under 45 atm H₂ at 30°C for 48 h, the R alcohol was obtained with 80% ee and 100% yield. Under such conditions, the turnover number was greater than 2400000, while the turnover frequency at 30% conversion was 2280000 h⁻¹ or 63 s⁻¹.

This high rate and chemoselectivity for the C=O function are caused by the nonclassical metal–ligand bifunctional mechanism (Figure 9). The hydrogenation involves a metal-hydride intermediate. Hydride transfer from the metal center to the carbonyl carbon atom has been considered to occur by a [2+2] mechanism. This reaction involves a Ru hydride species possessing an NH₂ ligand, whose hydridic Ru–H and protic N–H are simultaneously transferred to the C=O linkage via a six-membered pericyclic TS, thereby forming an alcoholic product directly, without formation of a metal alkoxide (Figure 9a). In this hydrogenation, the metal and the ligand participate cooperatively in the bond-forming and -breaking processes. A more detailed mechanistic model is given in Figure 9b. The 18-electron-RuH species reduces the ketone substrate by the pericyclic mechanism and the formal 16-electron Ru–amide complex reacts directly with H₂ in a [2+2] manner, or by a stepwise mechanism assisted by an alcohol and a base, to give back the reducing RuH complex. The reducing activity of the RuH species is generated by the hydrogen-bonding NH₂ end in the diamine ligand, which forms a fac relationship with the hydride ligand in the octahedral geometry. Neither ketone substrate nor alcoholic product interacts with the metallic center throughout the hydrogenation. The enantiofaces of prochiral ketones are differentiated on the molecular surface of the coordinatively saturated RuH intermediate. This notion is in contrast to the conventional mechanism for hydrogenation of unsaturated bonds that requires the metal–substrate π complexation.

This NH effect is common to the mechanism of Ru-catalyzed asymmetric transfer hydrogenation. Recently we found that [RuCl₂[(S,S)–YCH(C₆H₅)CH(C₆H₅)NH₂]–(η⁶-arene)] (Υ = O, NTs) complexes or their analogues catalyze asymmetric transfer hydrogenation of aromatic and acetylenic carbonyl compounds, by using a 2-propanol/alkaline-base system to give the corresponding 5 chiral alcohols of high enantiomeric purity, as generalized in Scheme 13. A formic acid/triethylamine mixture often serves as a better
reducing agent. Certain imines are also reduced enantioselectively by this method. The detailed experimental and theoretical analyses revealed that the transfer hydrogenation of carbonyl compounds with 2-propanol proceeds via a coordinatively saturated 18-electron complex, \([\text{RuH}((S,S)\text{-YCH(C}_3\text{H}_2\text{CH(C}_3\text{H}_2\text{NH})_3\{\eta^6\text{-arene}\})]\). The latter 16-electron Ru–amide complex dehydrogenates 2-propanol to regenerate the Ru-hydride species.

Figure 10. Metal–ligand bifunctional mechanism in asymmetric transfer hydrogenation catalyzed by \([\text{RuH}((S,S)\text{-YCH(C}_3\text{H}_2\text{CH(C}_3\text{H}_2\text{NH})_3\{\eta^6\text{-arene}\})]\). \(R = \text{alkyl or D}; \ Y = \text{O or NTs}\).

8. Toward Cerebral Molecular Science

The major goals of synthetic chemists and the chemical industry have been the efficient synthesis of known valuable compounds. Another, and perhaps more important, pursuit is the creation of new valuable substances and materials through chemical synthesis. Toward this end, mere chemical knowledge or technology is often insufficient and basic research through interdisciplin ary collaboration with scientists in other fields is needed. The recent progress in asymmetric synthesis has, in fact, spurred such endeavors which are directed toward the creation of molecularly engineered novel functions.

In the mid-1980s, we established the long-sought after three-component coupling synthesis of prostaglandins (PGs) illustrated in Scheme 14. The five-membered unit could be combined with the two \(C_1\) and \(C_6\) side-chain (\(\alpha\) and \(\omega\) side chains) units by organometallic methodologies. Our asymmetric methods play a key role in controlling the C(11) and C(15) OH-bearing stereogenic centers. The requisite (R)-4-hydroxy-2-cyclopentenone is conveniently prepared on a multikilogram scale by kinetic resolution of the racemate by
BINAP–Ru-catalyzed hydrogenation.\textsuperscript{[43]} The BINAL-H reagent is useful for asymmetric synthesis of the lower side-chain block.\textsuperscript{[93, 94]} This straightforward procedure is useful for the synthesis of not only naturally occurring PGs but also their artificial analogues.\textsuperscript{[93, 94]}

To explore applications to the science of the human brain, we collaborated with the research groups led by M. Suzuki (my long-term collaborator at Nagoya and now at Gifu University), Y. Watanabe (Osaka City University), and B. Längström (Uppsala University; Figure 11).\textsuperscript{[95]} After a long investigation, (15R)-TIC, a PGI$_2$-type carboxylic acid, was found to show strong, selective binding in the central nervous system, which thereby identifies the novel IP$_2$ receptor. Interestingly, this compound has the unnatural 15R configuration, although most biologically active PG derivatives have the natural 15S configuration. This discovery was made by an in vitro study using frozen sections of rat brain and frozen sections of rat brain and (15R)-[$^3$H]TIC as a probe.\textsuperscript{[96]} However, this radioactive probe is not appropriate for studies on living monkey or human brain, since $^\beta^-$ particles emitted from $^3$H can not penetrate tissues. Incorporation of $^{11}$C, a positron emitter with a short half-life of about 20 min and a high specific radioactivity, as a radioactive nuclide is essential for noninvasive studies using positron-emission tomography (PET). Positrons ($^\beta^+$) interact with free electrons in biological materials, and produce $\gamma$ rays that can penetrate tissues and are detectable outside the human body. However, this presents a new chemical problem. The $^{11}$CH$_3$ group must be incorporated in the final step of the synthesis of (15R)-TIC methyl ester, and the total time for synthesis, workup, purification, and sterilization should be less than 40 min because of the short half-life time of $^{11}$C. A student in my group at Nagoya made a concerted effort to achieve this and, eventually succeeded with a rapid Pd-mediated coupling of methyl iodide and tributyl(aryl)stannane (excess) which is applicable to the synthesis of (15R)-[$^{11}$C]TIC methyl ester.\textsuperscript{[99]}

This technology was then transferred to the PET Center at Uppsala. A very dedicated colleague in our team, M. Suzuki, volunteered to test this new artificial compound on himself. After being carefully examined, (15R)-[$^{11}$C]TIC methyl ester was injected into his right arm. The methyl ester was carried through his blood stream, passed through the blood-brain barrier, reached his brain, and was hydrolyzed to the free carboxylic acid, which was bound to IP$_2$ receptors in his central nervous system. Figure 12 shows the PET images of horizontal slices of his brain, from the lower to the upper portions. From this trial, a new receptor, IP$_2$, was found in various important structures of the human brain. Thus, (15R)-TIC and its analogues are expected to have effects on the brain and, in fact, do show a unique neuroprotective effect, which may be of clinical benefit. Primary cultured hippocampal neurons exposed to a high oxygen concentration display the morphological features of apoptotic cell death and (15R)-TIC effectively protects them against such oxygen...
9. Prospects for the future

Studies of molecular chirality have the promise to yield significant clinical, scientific, and industrial benefits in the future. A structurally diverse array of molecular substances exists. All molecules possess common characteristics, namely, fixed elemental composition, definite atomic connectivity, and some conformation. From such precise nanometer-scale structures, certain significant properties and functions emerge. Chemists can design and synthesize molecules at will, based on accumulated scientific knowledge. The practical synthesis of enantiomers with a defined absolute stereochemistry is one of the most significant areas of research. This endeavor is not only an intellectual pursuit but is also a fertile area for the development of beneficial technologies. Its utility is obvious, and ranges from basic scientific research at a sub-femtomole scale, as in the case of brain research described above, to the industrial production of high-value compounds in multithousand tons per annum quantities. Louis Pasteur stated in 1851 that “Dissymmetry is the only and distinct boundary between biological and nonbiological chemistry. Symmetrical physical or chemical force cannot generate molecular dissymmetry”. This notion is no longer true. The recent revolutionary development in asymmetric catalysis has totally changed the approach to chemical synthesis. This field is now still growing rapidly and I am certain that it will play a pivotal role in the development of the life sciences and nanotechnology in the 21st century.

The highest honor for me is to be recognized with the prestigious 2001 Nobel Prize in Chemistry. This honor must be shared with my research family at Nagoya and with many collaborators at other institutions. Asymmetric hydrogenation has been the life-long focus of my research, and my studies have relied largely on BINAP chemistry, which I initiated with the late Professor Hidemasa Takaya. Subsequently, BINAP chemistry was developed further in our laboratories at Nagoya, where Professors Masato Kitamura and Takeshi Ohkuma made major contributions. Other asymmetric hydrogenation methods were discovered during my directorship of the ERATO Molecular Catalysis Project (1991–1996), which was managed by Professor Takaaki Iwakura (now Institute of Technology) and Dr. Shohei Hashiguchi (Takeda Chemical Industry). Our laboratory at Nagoya is small. To realize the utilization of our scientific achievements, it was important to collaborate with other institutions. In this regard, I appreciate the cooperation of the groups led by Professors Sei Otsuka and Kazuhide Tani (Osaka University), and Professors Masaoaki Suzuki (Gifu University), Yasuyoshi Watanabe (Osaka City University), and Bengt Långström (Uppsala University). These are just the names of the leaders of the research groups, although many young associates and students also contributed significantly. I had opportunities to have fruitful collaborations with many other scientists whose names are cited in the references. We have been supported by many companies, particularly Takasago International Corporation and Teijin Company. The generous and consistent support from the Ministry of Education, Culture, Sports, Science and Technology was essential for the success of my research. I am also grateful to the Japan Science and Technology Corporation and many private foundations for their support. Last, but not least, I acknowledge Professor Hitosi Nozaki at Kyoto University, my mentor who first introduced me to this fascinating and rewarding field of research.

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[3] This interpretation must be considered carefully, because the R enantiomer racemizes in vivo.
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The ketone substrate reacts in an outer sphere of the coordinatively saturated 18-electron complex without interaction with the metallic center. Thus the general scheme given in Figure 1 is to be modified to some extent. For other mechanistic investigations, see: a) K. Abdurrashid, M. Faatz, A. J. Lough, R. H. Morris, _J. Am. Chem. Soc._ 2001, 123, 7473; b) R. Hartmann, P. Chem, _Angew. Chem._ 2001, 113, 3693; _Angew. Chem. Int. Ed._ 2001, 40, 3581.


This process has been used at Ono Pharmaceutical Co. for the industrial synthesis of PGs using the Corey method.


Catalytic asymmetric oxidations

Poland L. Rychnovský and Barry Sharpless have developed catalytic asymmetric oxidations, which utilize titanium in a single step. These reactions are useful intermediate products for various types of synthesis, including the production of drugs for reducing blood pressure.
In 1938, three years before I was born, a live coelacanth was taken from the waters off the eastern coast of South Africa. Previously known only in the fossil record from some hundred million years ago, the coelacanth and the implications of its discovery remained big news for years, and fueled an enthusiasm for “creatures” that persisted for decades. Those of us born in the 1940s grew up on photos of eminent scientists setting off on expeditions, their sunburned faces dwarfed by mountain explorers’ garb, or making thumbs-up signs as they entered the water in scuba gear. We shared their confident expectation that the Loch Ness Monster, Sasquatch, the Yeti—even adinosaur—soon would be taken alive.

I grew up loving the sea and loving fishing in particular, but unlike most fishermen I cared less for the size or quantity of the catch than for its rarity. Nothing could be more exciting than pulling (if not this time, surely the next!) a mysterious and hitherto unknown creature from the water. As a kid, I passionately wanted to be one who caught the next coelacanth, the first to see something that was beyond reasoning, even beyond imagining.

Opening a Nobel Lecture with a fishing expedition may seem frivolous, even indecorous, but I assure you no disrespect is intended. These are the circumstances that shaped my professional life: my first laboratory was New Jersey’s Manasquan River, whose astonishingly rich variety addicted me to discovery; a few years later, when I was as comfortable at sea as I’d been on the river, my laboratory became the Atlantic Ocean. Later, when I started doing chemistry, I did it the way I fished—for the excitement, the discovery, the adventure, for going after the most elusive catch imaginable in uncharted seas.

Chemists usually write about their chemical careers in terms of the different areas and the discrete projects in those areas on which they have worked. Essentially all my chemical investigations, however, are in only one area, and I tend to view my research not with respect to projects, but with respect to where I’ve been driven by two passions which I acquired in graduate school: I am passionate about the Periodic Table (and selenium, titanium, and osmium are absolutely thrilling), and I am passionate about catalysis.

What the ocean was to the child, the Periodic Table is to the chemist; new catalytic reactivity is, of course, my personal coelacanth.

Even though I grew up in Philadelphia, if someone asks me where I’m from, I usually say “the Jersey Shore”, because that’s where my family spent summers, as well as many weekends and holidays, with my father joining us whenever he

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**Searching for New Reactivity (Nobel Lecture)**

K. Barry Sharpless*

The processes for the selective oxidation of olefins have long been among the most useful tools for day-to-day organic synthesis. Herein, the focus is on the asymmetric-epoxidation (AE) and asymmetric-dihydroxylation (AD) reactions developed by Sharpless and co-workers. The reactions have a wide scope, are simple to run, and involve readily available starting materials. Ligand-accelerated catalysis is crucial to these reactions and might be the agent for uncovering more catalytic processes. In addition to the selectivity benefits of catalysis, the phenomenon of turnover (amplification) raises its potential impact. The author and his co-workers developed small, highly enantioselective catalysts that were unfettered by the “lock-and-key” selectivity of Nature’s enzymes, and tolerant of substrates throughout the entire range of olefin substitution patterns.

**Keywords:** asymmetric catalysis • epoxidation • hydroxylation • N ligands • Nobel lecture

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Asymmetric Oxidation

K. Barry Sharpless and his co-workers have discovered and developed many widely used catalytic oxidation processes, including the first general methods for stereoselective oxidation—the Sharpless reactions for asymmetric epoxidation, dihydroxylation, and aminohydroxylation of olefins. His mentors at Dartmouth College (BA in 1963), Stanford College (PhD in 1968 and postdoctoral research), and Harvard University (further postdoctoral research) were Prof. T. A. Spencer, Prof. E. E. van Tamelen, Prof. J. P. Collman, and Prof. K. Bloch, respectively. Before 1990, when he became W. M. Keck Professor of Chemistry at the Scripps Research Institute, Prof. Sharpless was a member of Faculty at the Massachusetts Institute of Technology (1970–77, 1980–90) and Stanford University (1977–80). Prof. Sharpless’s honours include the Chemical Sciences Award of the National Academy of Sciences (of which he is a member), the Roger Adams and Arthur C. Cope Awards from the American Chemical Society, the Tetrahedron Award, the King Faisal Prize, the Prelog Medal, the Wolf Prize, the Nobel Prize (2001), and honorary doctorates from five American and European universities. The Sharpless research group continues to search for new homogeneous oxidation catalysts and for transition-metal-catalyzed asymmetric processes.
friends were all mates, we naturally agreed that enticing fish to bite was the greatest challenge, but I alone felt that getting the strike was the most fun, even more exciting than landing the fish. I worked as a mate almost daily every summer, right up until the day before I set out from New Jersey, headed toward the biggest ocean and graduate school at Stanford University.

That was in 1963. In the spring of that year, my inspiring Dartmouth College chemistry professor and first research director, Tom Spencer, talked me into delaying entering Stanford specifically to work for E. E. van Tamelen, Tom’s own mentor at Wisconsin. The appeal of fishing was such that Tom, to my later regret, never succeeded in getting me to spend any summers working in his lab. In fact, even in graduate school, I expressed my ambivalence by continuing to fantasize about finding a boat out of Manasquan to skipper and by failing—this did not please v.T.—to do the simple paperwork required to renew my NSF predoctoral fellowship.

However, toward the end of my first year at Stanford, a serendipitous misunderstanding catalyzed the complete transfer of my passion (some would say my monomania) from one great science to another; from fishing to chemistry. Before leaving for a lengthy European visiting professorship, v.T. sent me to the library to look for reactive inorganic species that might produce interesting transformations of organic compounds. My first projects with v.T. were selective oxidation of polyolefins and titanium-mediated deoxygenative coupling of alcohols, and I was already primed to appreciate useful chemistry employing “strange” elements after selecting the Wittig Reaction from a list of suggested topics for my student seminar. The Wittig Reaction really engaged my enthusiasm, and I ingenuously concluded that finding new reactions other chemists could use looked like a lot of fun.

In any event, upon v.T.’s return, I discovered he had not intended for me to spend all those months immersed in the literature. While I had no research results to report, I did have a notebook filled with ideas and an eagerness to drop my line throughout the vastness of the Periodic Table. I don’t think I’ve gone fishing in the literal sense a dozen times since then!

From van Tamelen, a Gilbert Stork protégé, I inherited enthusiastic disdain for “safe” problems, deep admiration for traditional multistep organic synthesis, and awe before selective biological catalysis: studying the squalene oxide/lanosterol cyclase enzyme left me impressed by enzymic selectivity, but depressed by the difficulty of using enzymes for synthetic transformations. After getting a double dose of him in the classroom, Derek Barton became my model. At Dartmouth, Tom Spencer taught a course on conformational analysis, based on one he took at Wisconsin from William S. Johnson (Tom’s uncle, in fact), then I experienced the original at Stanford.[**] Being wet behind the ears, I took conformational analysis for granted; it was Sir Derek’s search for new reactivity that electrified me. A postdoc with Jim Collman (the only person, I concede, who gets more excited about chemistry than I do) ignited my interest in using simple metal complexes to develop catalysts (in the Collman lab, incidentally, I had the privilege of many hours at the blackboard with labmate Bob Grubbs). Then, before taking up my job at MIT, a postdoc with Konrad Bloch confirmed my hunch that impatience rendered me incompetent around enzymes. Konrad graciously let me start working on my own ideas when his were much too frustrating for me.

One other part of my background seems to have contributed to my chemistry. The first American Sharpless (“Shar-plaintext[1]” then) came to Pennsylvania in the 17th Century, not long after William Penn. My father was a practicing Quaker only as a child, but the values in our home were Quaker values, and I was educated in a Quaker school. The Quakers encourage modesty, thrift, initiative, and enterprise, but the greatest good is being a responsible member of the community—being useful. “Elegant” and “clever” were the chemical accolades of choice when I started doing research, just as “novel” is high praise now. Perhaps the Quakers are responsible for me valuing “useful” most.

So that is my background as a chemist. I’ve been accused of going too far, when I speculate that chirality fascinates me because I handled my umbilical cord in utero, but I’m quite sincere in proposing that the extraordinary training I received as a young chemist transformed an existing passion for discovering the unknown into the search for new reactivity, and that Quaker utilitarianism made the selective oxidation of olefins so appealing.

With respect to chemical reactions, “useful” implies wide scope, simplicity to run, and an essential transformation of readily available starting materials. Clearly, if useful new reactivity is the goal, the obvious strategy is investigating the

**[1]** This diversion into fishing as a metaphor for research could go on for pages; consider how, when a boat was hooking tuna—the catch of choice—word spread by radio and the competition converged from every compass point. The hot boat’s captain greeted this acknowledgment of his success with some anxiety; while he liked setting the other captains’ agendas and pleasurably speculating that the parties on the other boats were considering chartering him next time, the secrets of his success nonetheless required protection, so trolling speeds were lowered to sink the lures and prevent rubbernecks from identifying them, and red herrings (literally, on occasion!) were casually displayed on the fish box.

Isaak Walton and John Hersey devoted whole books to this metaphor, so indulge me for a few more sentences. The handy process versus product dichotomy that applies so neatly to much of human endeavor illuminates this fisherman–chemist comparison, too. Conventional wisdom places fly-fishing at the “process” end of the scale, while a “product” fisherman uses sonar to find a school before he bothers to get his line wet. Process person though I am, only the Manasquan River ran through my fishing days; trolling for the unknown always had more appeal than hooking a trout I already knew was there.

**[**] When teaching MIT undergraduates, I always said “The lights came on with conformational analysis”, without thinking where I picked up the phrase, but now I know: the previous Tetrahedron Prize article states “Just as chemists of the Robinson generation worked without concern for stereochemical factors so we, in the early days, were working in ignorance of conformational considerations until Derek Barton showed us the light in 1950”. The author is, of course, Bill Johnson (see reference [1]).
Asymmetric Oxidation

transformation chemists rely on. The processes for the selective oxidation of olefins have long been among the most useful tools for day-to-day organic synthesis because of these appealing characteristics of olefins:
1) they are among the cheapest functionalized organic starting materials, 
2) they can be carried “hidden” through conventional acid/base-catalyzed transformations, then “revealed” at will by adding heteroatoms through selective oxidations, 
3) most simple olefins are prochiral, and provide a prominent portal to the chiral world.

The trisubstituted olefin geraniol, in addition to being one of my favorite smells, provides an excellent case study both for laying out the challenges of selective olefin oxidation as well as for noting some benchmarks in meeting those challenges.

As shown in Scheme 1, geraniol (1) has two trisubstituted olefinic units, one of which has a hydroxy group in the allylic position. Four monoepoxides are possible: making either racemic 2 or racemic 3 requires regio- or chemoselectivity, while making each of the individual enantiomers requires enantioselectivity. When Henbest showed that the electronic deactivation by the oxygen substituent at C-1 causes peracids to prefer the 6,7-double bond (especially on the ester deactivation by the oxygens substituent at C-1 causes peracids derivatives), making racemic 3 impossible.

Two years later, the most scientifically stimulating and professionally gratifying collaboration of my career, the total synthesis of the eight L-DOPA synthesis that came out of Knowles’ Monsanto lab was the asymmetric hydrogenation of the first commercial application) sustained my faith that a catalyst for asymmetric oxidation could be found. Jack Halpern’s mechanistic studies on asymmetric-hydrogenation catalysis likewise inspired me. Several Japanese chemists, chief among them Ryoji Noyori, hugely extended both the scope and application of the asymmetric hydrogenation process.

This focused search has frustrated but never bored me, even after so many years, and the geraniol paradigm illustrates why.

In 1970, Bob Michaelson cracked the other half of the regioselectivity problem presented by geraniol. Since early-transition-metal-catalyzed epoxidations with alkyl hydroperoxides were highly selective for the 2,3-position, racemic 2 could be prepared as well.

In 1980, Tsutomu Katsuki discovered the titanium-catalyzed asymmetric epoxidation (AE); the enantioselective oxidation of olefins bearing allylic hydroxy groups made it possible to make either 2 or ent-2, which thereby solved one side of the enantioselectivity problem.

The osmium-catalyzed asymmetric dihydroxylation (AD), discovered in 1987, subsequently was improved to the point that either 3 or ent-3 could be made by way of the diol, an indirect solution to enantioselective epoxidation at the 6,7-position (Scheme 2).

In 1990 came the breakthrough introduction of enantioselectivity into existing manganese—salen ligand catalysts for the epoxidation of isolated olefins. Developed independently by the groups of Jacobsen and Katsuki, these epoxidation catalysts work best on only a few of the six olefin-substitution classes. Nonetheless, their very existence is tantalizing, and encourages the hope that a general, off-the-shelf solution will be found for the direct asymmetric-epoxidation reaction across the full range of isolated-olefin substitution patterns.

The greater generality of man-made catalysts, such as these catalysts, compared with enzymes was noted first by Knowles and Kagan. During the lean times in the first decade of my career, their pioneering development of man’s first highly enantioselective catalysts (the L-DOPA synthesis that came out of Knowles’ Monsanto lab was the asymmetric hydrogenation’s first commercial application) sustained my faith that a catalyst for asymmetric oxidation could be found. Jack Halpern’s mechanistic studies on asymmetric-hydrogenation catalysis likewise inspired me. Several Japanese chemists, chief among them Ryoji Noyori, hugely extended both the scope and application of the asymmetric hydrogenation process.

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My own investigations into the oxidation of olefins commenced at MIT in 1970, but, fittingly, I was back at Stanford on January 18, 1980, for Tsutomu Katsuki’s dramatic discovery of the titanium-catalyzed asymmetric epoxidation. Two years later, the most scientifically stimulating and professionally gratifying collaboration of my career, the total syntheses of the eight L-hexoses with my MIT colleague Sat Masamune, capped the AE’s discovery. Previous articles in a vein similar to this one describe that chemistry; understanding the AE’s significance and putting that understanding to work are the purview here.

After the euphoria of completing the hexose syntheses, three years were spent developing, refining, and finding more applications for the AE. During this time I returned to the
search for new reactivity, but it was clear that my random, scattershot attempts were going nowhere,[*] so I was grateful for the opportunity to spend the first three months of 1987 as a Sherman Fairchild Scholar at Caltech.

Many universities and institutions have handsome Fairchild buildings, but Caltech, ever the bastion of collegiality and camaraderie, used its Fairchild grant to endow a program that brings scientists from many fields to be housed graciously in the sunshine for as long as a year. Since my research group’s investigation of the AE had reached the point of diminishing returns, I left for Pasadena hoping to renew my mission. I love reading journals, and I love mountains, so the Caltech library with its panoramic view of Mount Wilson became my thinking place of choice. Every day Mount Wilson offered new vistas, especially on those occasions when snow fell during the night. One morning, the mountain was completely cloaked (the first time a freezing temperature was recorded in downtown LA, I recall), and the melting snow receded at such a clip that I was sure I saw it happening. Mount Wilson was the perfect backdrop for bringing my own big picture back into focus, and I returned to MIT eager to renew my search for new reactivity. Meditating on the AE yielded this lesson to guide that search: Ligand-accelerated catalysis (the significance of which is documented in M. G. Finn’s fine MIT thesis on the mechanism of the AE[*]), is crucial to the AE and not merely a feature of it; despite its rarity, this phenomenon might be the agent for uncovering more catalytic processes.

Of course, the first and best-known example of ligand acceleration is found in Criegee’s papers from the 1930s.[14] He observed that pyridine accelerates the reaction in his classic study of osmium tetroxide and olefins. Ironically, the lesson from the AE was directing me back toward Criegee, whose discoveries in olefin oxidation and osmylation were, in large measure, the jumping-off point for my own research career. I first looked into Criegee’s process shortly after becoming an assistant professor at MIT. My attraction to the reaction of OsO₄ with olefins was inevitable. Osmium tetroxide not only accomplishes an important synthetic transformation, but it does so with a scope and reliability unique among reactions used for organic synthesis. It reacts only with olefins and it reacts with all olefins (slight poetic license here). Even R. B. Woodward valued Criegee’s stoichiometric transformation so much he was willing to use 100 g of OsO₄ in one shot. Osmium’s expense was not compatible with “useful,” however and, since the existing catalytic variants were not very effective, I started searching for a reliable catalytic method. In 1975, Kagayasu Akashi found a good process for us, based on a hydroperoxide as an oxidant, tertiary-butyl hydroperoxide (TBHP),[15] but the brass ring was ultimately captured that same year with the publication of the famous Upjohn process based on N-methyl morpholine-N-oxide (NMO).[16]

Throughout the rest of the 1970s, osmium remained our primary tool for looking for new reactivity. We discovered that imido osmium(viii) species effectected stoichiometric cis-oxygenation of olefins in direct analogy to the cis-dihydroxylation of olefins by osmium tetroxide; even more effective catalytic versions of those transformations came shortly thereafter.

In 1977 I left MIT, where I had been a contented member of a wonderful chemistry faculty since 1970, for Stanford University, where I previously spent six contented years as a graduate student and postdoc, surrounded by a wonderful chemistry faculty. I never made the transition back to contentment at Stanford, probably because my research wasn’t churning up much. This frustrated me and scared off potential graduate students who wanted publications, not a fishing expedition. In addition, at Stanford I remained awed by a faculty I worshiped when a graduate student, and I lacked the confidence to stand firm on issues, particularly faculty appointments, that meant a lot to me. In 1979, at about the same time I made the decision to return to MIT, Steve Hentges, who worked in our well-developed osmium imido area and already had the material for a good Ph.D. thesis in hand, decided to take on one more project before writing up. The notion of an asymmetric ligand for osmium tetroxide had been knocking around the lab for years, and Steve first approached the idea by making several pyridines with chiral substituents at the 2-position; these gave diols with essentially 0% ee.[17] Pyridine is only a modest ligand for osmium tetroxide, and, as we discovered, any ortho substituent is

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[*] I have enormous admiration for colleagues who can keep multiple research projects alive and large groups humming, but the “monomania” that prevents me from being able to do that is my long suit as well, making it possible to concentrate—for years, actually—on a single topic. I know some chemists call my approach “intuitive,” a term I’ve always thought underestimates the rigor that frames my method; perhaps “unstructured” or “contemplative” is more accurate. Many of my cohorts are quick and facile and can jump on a few interesting bits of data and start building tentative edifices that get taken apart and reassembled to suit new data. I, on the other hand, am ruminative: my training after all consisted of busily poking and perturbing the Manasquan River, a curriculum both urgent and leisurely, one that permitted exploration without assumptions and without the structure imposed by deadlines or competition, or by knowing too little or too much. Since I was compelled by shyness to learn to do much on my own, there was (and is) no right or wrong way, only many ways, some more or less suited to a given endeavor. The discipline, nonetheless, is exacting; everything that can be observed should be observed, even if it is only recalled as the bland background from which the intriguing bits pop out like Venus in the evening sky. The goal is always finding something new, hopefully unimagined and, better still, hitherto unimaginable. When I became a bench- and desk-bound explorer, the method stayed the same. I try to imagine away the packaging the information arrives in, then let bits and pieces move around lazily, rather like objects tumbling slowly in zero gravity, but eventually, over time, exploring every possible relationship with other information that’s previously arrived. Since joining the faculty of The Scripps Research Institute, I’ve discovered that ocean swimming and running on the beach provide an excellent medium for this kind of activity. However, in any climate, the best catalyst is generous, stimulating conversation. This slow, but endlessly fascinating, method is like an exotic ritual courtship, full of displays of bright feathers or offerings of shiny metal or towers of sticks—what does it all, what does any of it mean? Enormous concentration is required to remember it all in a way that causes little sparks when certain conjunctions appear, making a connection with something noted previously, perhaps decades ago. Sadly, as I grow older, the connections become harder to summon up, so the sparks, though they seem as bright as ever, are less frequent. I describe this process at length because it’s not the way most scientists approach their work, nor is it well suited to the demands of funding agencies that are railroaded into answering questions posed for political rather than scientific reasons, nor to the needs of graduate students who require publications to compete for jobs. Academic chemistry is much harder now, and I’m glad I was born when I was.
lethal to binding. But since William Griffith at Imperial College had shown that quinuclidine binds much more strongly to OsO₄, I suggested trying the cinchona alkaloids, essentially substituted quinuclidines.[14] (Many chemists have expressed surprise at how quickly we arrived at what is now the best ligand framework for the AD: anyone with a natural products background and who is also a fan of Hans Wynberg’s chemistry recognizes the cinchona alkaloids as the obvious next step.) The results were spectacular, even without taking into account a measurement error (discovered years later) that caused most of the ee values to be underreported by 5–15%.[17]

Steve had a dramatic story to cap his thesis work, so he started writing; my attention was taken up by the decision to return to MIT. Then, a couple of months later, Katsuki discovered an asymmetric process with ingredients so cheap it made working with osmium look like Rolls-Royce chemistry. Although the AE was only weakly catalytic in the early days,[19] its uniformly high ee values and nontoxic, inexpensive reagents were enough to completely divert our attention from its promising but stoichiometric predecessor, the OsO₄/cinchona asymmetric dihydroxylation.

The preceding paragraph has no doubt failed to deflect your attention from the obvious question: Why didn’t I write the Hentges ligands in the Upjohn system in 1979? Indeed, why did I propose the experiment in my NIH grant renewal in January, 1984, but not follow up on it? “As for the ligand,” I wrote in the proposal, “it is probably best to stay with the cinchona derivatives because the quinuclidine moiety is the best ligand we know of for Os¹VIII complexes. The substrate will be stilbene...the osmium catalyst will be recycled using an amine N-oxide. Ideally, both the osmium and the chiral alkaloid could be used in catalytic quantities. A successful system of this type could be of great practical importance.”

Instead of poking and perturbing, the Jersey Shore School of Thinking’s cardinal rule, I stuck with the odds logic suggested: ligands accelerate the reaction of OsO₄ with olefins, but they also bind avidly to the resulting osmate ester, and lethally affect catalyst turnover. This ability of ligands, such as pyridine and quinuclidine, to kill turnover in catalytic-osmylation systems had often been observed in my laboratory. What I did not, nor could not, anticipate is the perfect balance cinchona alkaloids achieve in ligating ability: they bind well enough to accelerate the key step, but weakly enough to slip off allowing the hydrolysis/reoxidation steps of the catalytic cycle to proceed. At the time, however, the precedents seemed clear, so the AD languished until 1987.

Unraveling the mechanism of the AE was largely the work of M. G. Finn.[15] His persistent exploration during the early to mid-1980s of the AE’s titanium–tartrate-catalyst system exposed a complex mixture of species in dynamic equilibrium with one another.[20] M. G. discovered the main species [Ti(dipt)(O-Pr)₄] (DIPT = diisopropyl tartrate) is substantially more active than the many other species present (significantly, it is five to ten times more active than Ti(OR)₂, a catalyst for the formation of racemic epoxy alcohol) and this rate advantage funnels catalysis through the appropriate tartrate-bearing species.

If the tartrate-induced acceleration of the titanium-catalyzed epoxidation reaction came as a surprise, investigating that phenomenon brought even more surprising results. We ultimately found 24 metals other than Ti that catalyze the epoxidation of allylic alcohols by TBHP (Figure 1), but all these systems were strongly inhibited or killed by adding tartrate.[21] Ligand-decelerated catalysis was clearly the rule, while ligand acceleration was the extraordinarily valuable exception.

![Figure 1. Metals catalyzing the epoxidation of allylic alcohols by TBHP. Adding tartrate ligand always affects reactivity: the titanium system is accelerated.](image)

Shortly before I left for Caltech, Chris Burns, encouraged by Pui Tong Ho, presciently lobbied to resurrect the OsO₄/cinchona asymmetric dihydroxylation, and, without any encouragement from me, I must admit, he embarked on the synthesis of a stoichiometric C₇-symmetric ligand for the AD.[22] A few months later, I too was again committed to osmium, and when Bill Mungall and Georg Schröder reexamined the work from 1979, they uncovered ee values even better than previously reported. Meanwhile, Eric Jacobsen attacked the problem from the mechanistic side, and discovered that the ligand-dependent rate accelerations could be enormous.[23]

With these very encouraging results on the stoichiometric reaction just in, István Markó joined the project. I was traveling at the time, and on his own initiative, unaware of the NIH proposal, he combined Hentges’ system[17] with the reliable Upjohn NMO-based catalytic-osmylation system,[16] immediately getting results indicating the reaction was catalytic.[24] However, unlike the dramatic “Eureka!” that accompanied the discovery of the AE, cautious optimism was the response to the catalytic AD and its initially modest ee values. Now, however, after years of research since Markó’s first experiments in October of 1987, the AD’s utility rivals and often surpasses the AE’s.[25] Unlike the AE, for which
Katsuki’s initial tartrate-ester ligands have yet to be eclipsed, the ligands for the AD have evolved substantially in effectiveness and scope, through substitution at the C-9 hydroxy moiety.

The simple ester derivatives (e.g. the acetate and para-chlorobenzoate esters) gave way in 1990 and 1991 to aryl ether derivatives, first proposed by Yun Gao during a late-night group meeting to address the mechanistic question of a possible ligating role of the ester carbonyl. Brent Blackburn made the phenyl ether which, to our surprise, gave good ee values, but was too hard to make to be competitive with the then dominant para-chlorobenzoate (CLB) ligand.

Almost a year later, Declan Gilheany correctly predicted that aryl ethers should be better for aliphatic olefins than the CLB ligand,[25] and these results laid the foundation for a steady expansion of this ligand class, which culminated in the phenanthryl ether ligand,[26] Another big jump in effectiveness came with the dimeric alkaloid ligands having a phthalazine core, first made by Jens Hartung in 1990.[27] Along with the pyrimidine ligands[28] whose development they inspired, they remain the best general ligands for the AD reaction.

The search for better ligands was paralleled by advances in catalyst turnover efficiency:
1) John Wai found both the second-catalytic-cycle problem and its partial remedy; slow addition of the olefin.[29]
2) Since ferricyanide in tert-butanol/water provides an excellent two-phase system for catalytic osmylation,[30] Hoi-Lun Kwong applied it to the AD, which solved the second-cycle problem and the need for slow addition.[31]
3) Willi Amberg found that adding organic sulfonamides greatly facilitates the rate of catalyst turnover for olefins whose osmate esters resist hydrolysis.[32]

As the practicality (it has been scaled up to run in 4000-liter reactors with no ill effects on yield or ee value[33]) and scope of the AD process grew, so did the pressure to understand the origin of its enantioselectivity. Mechanistic studies dating from the 1970s by Alan Teranishi and Jan Bäckvall[34] were rekindled by Eric Jacobsen in 1987 and continued into the mid-1990s.[14]

While a complete and general solution to the geraniol paradigm’s final challenge is clearly within reach, comparing selectivity at the bench with selectivity in living systems remains striking. For example, the squalene monoxygenase in our livers unerringly deposits a single oxygen atom on the squalene molecule and, in so doing, further chooses only the si-enantioface of the terminal double bond (Scheme 3).[35] On the other hand, the attempted AD of a single double bond of squalene does give the terminal diol in 96% ee. The preference for the terminal double bond is slight, however, and internal diols as well as tetraols also can be isolated from the reaction.[36] Thus, while the AD catalyst cannot match the exquisite selectivity of the enzymic system, this very inability to discriminate between the six trisubstituted double bonds of squalene allows the exhaustive AD of squalene (Scheme 4) in an overall yield of 79.8% for the AD-β reaction.[37]

Serial multistep reactions such as these are generally stymied by Bob Ireland’s “arithmetic demon”—the geometric fall in yield in sequential chemical reactions. The AD of each double bond is one step in a procession of six dihydroxylations, each with a chemical and an optical yield, twelve yields in all. Thus the average yield of each step is (0.798)^12 or 98%, which translates to 98% for each chemical yield, 96% ee for the single enantioselective reaction and 96% de for each of the five diastereoselective reactions. The high yield of a single enantiomer from the multiple hydroxylation events required to oxidize squalene completely reflects the reliability and selectivity of the AD process. Joel Hawkins’ Berkeley lab kinetically resolved the chiral fullerene C_{70}, which resulted in the first enantiomerically pure allotrope of carbon, the AD’s most intriguing use to date.[38]

My decision, nearly 25 years ago, to study the selective oxidation of olefins produced an unexpected bonus, one that gave me an opportunity to investigate uncharted territory on a scale that is more associated with the previous half-century than with our own. Selenium, titanium/alkyl peroxides, and osmium, my three most successful olefin oxidation catalysts, all had phobias associated with them, with the result that much of their chemistry remained terra incognito. Selenium and osmium were considered highly toxic, and the peroxide oxidants used with titanium had a nasty reputation. Rarely did I find myself in another chemist’s territory; likewise, few wanted to cast a line in mine.

Tracking these elements offers a rather curious way to view my research. Figure 2a plots the time course of their
dominance (as measured by publications, for want of a more qualitative ruler) during the years 1970–1993. Selenium came first, flourished, then ended abruptly. Osmium research came next, coexisting with selenium until both were eclipsed by titanium, the descendant of molybdenum and vanadium. Osmium made a strong comeback, knocking off titanium.

Figure 2b, which charts my research with respect to catalytic transformations, looks quite unlike Figure 2a, but relates directly to it. As my involvement with catalysis grew, the largely stoichiometric selenium reagents lost their appeal; titanium fell because the effectiveness of the titanium catalyst for the AE is modest, with about only 20 turnovers per titanium center before all activity is lost. Osmium, despite a bimodal presentation, was never actually out of the picture, merely quiescent until the discovery of the highly catalytic AD (it has been run to completion with as little as 1/50,000 of osmium catalyst).

In Figure 2b, the only real deflection from the steady growth of catalysis to dominion in my research was the 1982 trough caused by the hexose synthesis collaboration with Sat Masamune. Stepping out of the realm of catalysis is almost unimaginable to me now.

Because of its unique potential for channeling a reaction sequence along one of myriad possible pathways, selective catalysis lies at the heart of both pure and applied chemistry, not to mention life chemistry. In addition to the selectivity benefits of catalysis, the phenomenon of turnover (which equals amplification), implicit in the definition, highly leverages its potential impact. For all these reasons, catalysis was and continues to be the engine driving my research.

Nature’s enzymes made it possible to imagine simpler asymmetric catalysts. What we found, however, was unimaginable on two scores: small, highly enantioselective catalysts that were not only not fettered by nature’s “lock-and-key” modus operandi, but tolerant as well of substrates throughout the entire range of olefin substitution patterns. Now, going on four decades later, I am still plumbing the vastness of the Periodic Table in search of new catalylic reactivity. The unpredictability and rarity of what I seek are not deterrents since I am, after all, the product of optimistic times. There are other coelacanths to be found!

Above all I thank and express my deep gratitude to my past and present co-workers at MIT, Stanford, and The Scripps Research Institute. Many of you learned to tolerate my style of directing research (an oxymoron perhaps?); indeed, some of you flourished. Others were not well served, and to you I sincerely apologize. I’m exceedingly proud of the MIT undergraduates who got their feet wet in my lab and now hold leading academic and industrial positions: remember you got your opportunities because Tom Spencer gave me mine, and I expect you to do the same. Mentioning Tom brings me back, as so many things do, to E. E. van Tamelen; the bright flashes of his career remain of the first magnitude and still inspire me. And finally, my scientific career would have been unthinkable without the constant support and counsel of my wife, best friend—and ghost writer—Jan.

I also thank the National Institute of General Medical Sciences, National Institutes of Health (GM-28384) and the National Science Foundation for their continuous financial support over the past 25 years and, more recently, the W. M. Keck Foundation and the Skaggs Institute for Chemical Biology for helping to make possible my present tenure at The Scripps Research Institute in La Jolla.

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Figure 2. a) Selenium, titanium, and osmium chemistry; note the osmium line’s bimodality. b) Growth of catalysis in my laboratory. n = number of publications; P = percentage of publications.
Five years later, Bob Hanson made the simple but wonderful discovery that adding molecular sieves to the reaction dramatically increases catalyst turnover, so that the AE process became truly catalytic. R. M. Hanson, K. B. Sharpless, J. Org. Chem. 1986, 51, 1922.

Steve Pedersen provided invaluable structural results to aid M. G. Finn’s studies during this period. Steve’s work gave us our first glimpse into the dynamic world of complex mixtures in rapid equilibrium with each other. His contributions are summarized in: K. B. Sharpless, Chem. Soc. 1987, 27, 521. These studies led to no new catalysts, but they drove home our appreciation for the absolute need for a ligand-acceleration effect in catalyst systems where ligand exchange is rapid.


The reaction of an aryl or vinyl boronic acid with an aryl or vinyl halide catalyzed by a palladium(0) complex, which was first published in 1979 by Akira Suzuki, was a major breakthrough in organic chemistry and laid the foundation for a wealth of new catalytic organic reactions.
Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C–C Bonds (Nobel Lecture)**

Akira Suzuki*

Biography
I was born on September 12, 1930 in Mukawa, a small town in Hokkaido, Japan. I attended the primary school there and entered secondary school at Tomakomai, where we had one of the biggest paper companies in Japan. During my high school, I was interested in mathematics. Consequently, when I entered Hokkaido University in Sapporo, I was thinking of studying it. In the junior course, I became interested in organic chemistry by reading the book “Textbook of Organic Chemistry,” written by L. F. Fieser and M. Fieser. Finally, I decided to major in organic chemistry.

The title of my doctoral thesis was “Synthesis of the Model Compounds of Diterpene Alkaloids”. In the study, I used organometallic compounds, Grignard reagents, and organozinc compounds as synthetic intermediates, and I perceived that such organometallic compounds are interesting and versatile intermediates for organic synthesis. After I completed the PhD program at the Graduate School of Science, Hokkaido University, in 1959, I was employed as a research assistant in the Chemistry Department. In October 1961, after two years and six months, I was invited to become an assistant professor of the Synthetic Organic Chemistry Laboratory at the newly founded Synthetic Chemical Engineering Department in the Faculty of Engineering. In April 1973, I succeeded Professor H. Otsuka at the Third Laboratory in the Applied Chemistry Department. In total, I have spent 35 years at Hokkaido University as a staff member—two and a half years in the Faculty of Science, and another thirty-two and a half years in the Faculty of Engineering. Other than about two years of study in America, and a few months at other places overseas, most of my life has been spent at the Faculty of Engineering. Including my nine years as a student, the majority of my life has been at Hokkaido University. After my retirement from Hokkaido University in 1994, I joined two private universities in Okayama prefecture—Okayama Science University and Kurashiki University of Science and Arts—and I retired from the universities in 2002. In the following I would like to describe a few memories of my life in chemistry.

Professor Herbert C. Brown and Purdue University

As I reflect on these long years, I see that there were many difficult periods as well as joyful ones. Memories of the tough, trying experiences tend to fade with time. I think now mainly about the fun things, and I will describe a few memories that I have from my work.

It was on a Saturday afternoon in 1962. I visited the Maruzen bookstore in Sapporo. As I browsed the chemistry books, I discovered a very unacademic looking volume, bound in red and black. This book was Hydroboration by H. C. Brown, the 1979 Nobel Laureate in Chemistry. I took the book in my hands, and began looking through its pages to find words written in Professor Brown’s unique style. I purchased the book and returned home. I can still remember clearly how I picked it up after dinner that evening, and could not put it down. It is not very long, but it remains as one of the few scholarly books which I have stayed up all night to read. At the time, I had just transferred to the Faculty of Engineering from Science, and I wanted to begin research in a new area at my new workplace. This is perhaps one reason why this book had such an impact on me.

Inspired by this experience, I went to Purdue University in Indiana in the August of 1963 (Figure 1) and spent almost two years at Professor Brown’s laboratory researching the newly discovered hydroboration reaction as a postdoctoral research associate (Figure 2). It was my first time in a foreign country, and one of the things that left an impression on me was the strength that America had at that time. For instance, one American dollar was worth 360 yen. My monthly salary as a doctoral researcher was four times what I received even as an assistant professor in Japan. There was little difference in the food between the rich and the poor. There were many such things that I found that were unimaginable in Japan. Purdue University has a strong relationship with Hokkaido University. In the past, the former president of the university, Professor S. Ito, had studied at Purdue. Professor S. Nomachi and Professor T. Sakuma were at Purdue at the same time as I was.

From Professor Brown I learned many things, including his philosophy towards research, but there is one thing he said that I can recall with clarity: “Do research that will be in the textbooks”. It is not easy to do this kind of work, but this has remained my motto. Professor Brown was 51 years old, and he

[**] Copyright © The Nobel Foundation 2010. We thank the Nobel Foundation, Stockholm, for permission to print this lecture.
was an extremely active researcher. He visited Hokkaido University three times. I had the opportunity to meet him and Mrs. Brown more than ten times (Figure 3), but we missed them in 2004 and 2005, unfortunately.

Hydroboration is the reaction of alkenes with borane to produce organic boron compounds. These boron compounds differ from other organometallic compounds: they are chemically inactive, particularly in ionic reactions. For example, organic boron compounds are stable in the presence of water and alcohol, and do not undergo Grignard-type reactions. Therefore, it was thought that such compounds would be unsuitable as synthetic intermediates. Between 1963 and 1965, when I was at Purdue, there were more than 30 doctoral researchers and graduate students from all over the world in the Brown Lab. Many of these friends shared the opinion that the boron compounds were inactive. In contrast, I thought that the stable character of organoboron compounds could be an advantage in some cases. For example, we could use these compounds in the presence of water without any special care. I decided that there might be some way to use these compounds in organic reactions, and I created a new research plan upon my return to Japan in April 1965 (Figure 4).

Discovery of Alkyl Radical Formation from R3B

At the time, I focused on three characteristics of organoboron compounds. First, compared to other organometallic compounds, the difference in the electronegativity of the C–B bond is small, meaning that it is an almost perfect covalent bond. Second, the boron atom has an open π-electron structure, meaning that it might be susceptible to nucleophilic reagents. This suggested that the compounds might undergo reactions as shown in Equation (a). Third, studies of the C–B

\[
\begin{align*}
\text{B-R} + \text{X-Y} & \Rightarrow \text{B-X}_R^\bullet + \text{Y}_R \quad \text{(a)}
\end{align*}
\]
In consideration of these three points, I decided to study the reaction of organic boron compounds with \( \alpha,\beta \)-unsaturated ketones. In other words, I hypothesized that intermediate (I) in Equation (b) would be obtained through a quasihexagonal transition state, which would be hydrolyzed to give a saturated ketone. When we examined methyl vinyl ketone in the reaction, we found that the predicted corresponding saturated ketone was produced in a quantitative yield [Eq. (b)]. We obtained these results in 1966, and I notified Professor Brown of our findings in a letter, and he was extremely interested. He told us that he wanted to explore the results at Purdue as well. I supported his proposal, and we continued to study \( \alpha,\beta \)-unsaturated ketones at Hokkaido, while \( \alpha,\beta \)-unsaturated aldehydes would be investigate at Purdue. We analyzed the scope of the reaction, and tried several types of \( \alpha,\beta \)-unsaturated ketone reactions and found that each produced favorable amounts of the corresponding saturated ketones at room temperature. Although we discovered that compounds with a substituent in the \( \beta \) position, such as compounds II, would not react at room temperature, we found that the expected proportions of products could be formed in THF (tetrahydrofuran) solution at reflux temperature. I received a letter from G. Kabalka (now professor at the University of Tennessee), who was then a graduate student doing related research at Purdue. According to the letter, something similar was found for \( \alpha,\beta \)-unsaturated aldehydes. None of the corresponding saturated aldehydes were produced by the reaction of compounds such as III, which had a substitution group in the \( \beta \) position, even though many similar compounds such as acrolein reacted easily at room temperature. I proposed that each laboratory confirm the results of the other, and we began experiments on III and found that the reaction proceeded in THF at reflux temperature. However, subsequent experiments at the Brown lab did not find that our reaction occurred. I remember a sentence in the letter I received from Professor Brown reporting their results. “Chemistry should be international. Why do we have such a big difference between two places, Sapporo, Japan, and West Lafayette, USA?”

When we looked more closely at these contradictory results, we discovered something quite unexpected. A trace amount of oxygen contaminating in the nitrogen gas we used in our reaction system was catalyzing the reaction. At the time, we knew that organoboron compounds reacted with oxygen, so both we and the Brown Lab conducted the reactions in nitrogen gas. In our laboratory, we used nitrogen purchased from Hokkai Sanso (now called Air Water Inc.), which we further purified. Nevertheless, trace amounts of oxygen were still present in our nitrogen gas. The oxygen acted as a catalyst and promoted the reaction. In the USA, extremely pure nitrogen could easily be purchased in those days, and the nitrogen gas did not contain sufficient amounts of oxygen to cause the reaction.

From such unexpected results, we found that with small amounts of oxygen catalyst, organoboron compounds would produce alkyl radicals. Furthermore, the reaction followed the radical chain mechanism as shown in Equation (c), rather than the coordination mechanism that we had inferred previously [Eq. (b)].

\[
\begin{align*}
\text{B-R} + \text{O}_2 & \rightarrow \text{RCH}_2=\text{CH}_2 \rightarrow \text{RCH} = \text{CH}_2 + \text{H}_2\text{O} \\
\text{B-R} & \rightarrow \text{RCH} = \text{CH}_2 + \text{H}_2\text{O} \rightarrow \text{RCH}_2=\text{CH}_2
\end{align*}
\]

Serendipity

One often hears lately of the idea of “serendipity” in research. Serendipity refers to the capability to discover the crucial and essential components from unexpected phenomena. I believe that any researcher has the chance to exhibit serendipity. However, in order to make the most of such opportunities, a researcher must have the humility to see nature directly, an attentiveness that does not let even the dimmest spark escape, and an insatiable appetite for research. Some amount of luck also matters, but what can be said with certainty is that little will come of a half-hearted effort.

Quick Publication

In 1970, we were performing experiments to directly produce carboxylic acid from organoboron compounds. One possibility we explored was to use complexes derived from organoboron compounds and a cyanide ion which react with protonic acids. We were not able to obtain our intended result, but we discovered that these cyano complexes could produce symmetrical ketones in good yield when reacted with electrophilic reagents like benzoyl chloride. Nonetheless, I was busy preparing for a presentation at an international conference to be held in Moscow in 1971, and we left for the conference without finishing our paper on it. After I had successfully given my invited lecture, I left the lecture hall to quench my thirst with a glass of water. At that time, a tall foreign man introduced himself to me. That man was Professor A. Pelter of Manchester University in the UK. He later transferred to the University of Wales, Swansea, and served as the chair of the Department of Chemistry as well as the Vice-Chancellor of the university. At our first encounter in Moscow, I had no
idea that he was studying organoborane chemistry. We spoke about many things that day and, to my surprise, I learned that he had also performed the very research that we had just done, and had already published his results the previous month in Chemical Communications. As a result, our work remains unpublished. Today, that reaction is sometimes called the Pelter reaction. Knowing about our situation, Professor Pelter sympathized with us and consoled us, but no one else knew anything about it. We learned from it. When doing research, we must keep three things in mind. First, we must study the existing literature carefully and comprehensively. Second, we need to be aware that other researchers, near and far, are thinking about the same things that we are. Third, we must quickly publish papers on our results (not just oral presentations).

Tragic Accident

Thinking back on that conference—the International Conference on Organo-Metallic Chemistry in Moscow 1971—I cannot help but think of the tragic accident, in which an ANA passenger jet collided with a Japan Self-Defense Force aircraft in the skies above Shizuku-ishi in Iwate prefecture. On that day, I had flown from Sapporo/Chitose to Tokyo/Haneda to stay for one night before boarding an Aeroflot plane to Moscow the next day. I flew on a Japan Airlines flight in the afternoon, with no idea that the plane that departed only thirty minutes earlier would be involved in such a terrible accident. Knowing nothing of the tragedy, I landed in Haneda, and headed to the Haneda Tokyo Hotel near the Airport, and then learned of the accident. All passengers and crew, 162 persons, were killed.

Haloboration Reaction

Thereafter, our group carried out research on the synthesis of organic compounds through haloboration. I had one memory from this that I will reflect upon. This research was based on the discovery that a certain type of haloborane derivative adds to terminal carbon–carbon triple bonds. This reaction was discovered in 1981, but we first disclosed part of this research in the United States in 1982. That fall, the American Chemical Society hosted a symposium in Midland, Michigan, on organic synthesis involving organoboron compounds. I was one of the special invited speakers, and was preparing to travel to the US when I received a letter from Professor Brown. It was an invitation to visit Purdue to give a lecture before the symposium. The topic of that lecture was haloboration. Professor Brown listened to my presentation intently, and raised his hand to comment the moment I finished speaking. He said that his group had studied the possibility and usefulness of the same reaction at almost the same time as we had. They had looked at haloboration reactions for acetylene compounds, but they had only looked at reactions of the internal acetylenes as substrates. Their work was unsuccessful, and they ended the research. The goddess of fortune is capricious, indeed.

Over many long years, I have had many different experiences. I have encountered many friends at the Faculty of Engineering, Hokkaido University, especially among many of the people who continue to work at the Third Laboratory of the Applied Chemistry Department, and the Organic Synthetic Chemistry Laboratory in the Synthetic Chemical Engineering Department. They have allowed me to enjoy a long career in research. I conclude by expressing my sincere gratitude to these students and colleagues in research.

I have won several awards for my work, listed below:
- The Chemical Society of Japan Award, 1989.
- Japan Academy Award, 2004.
- The Order of the Sacred Treasure, Gold Rays with Neck Ribbon, 2005.
- The Order of Culture of Japan, 2010.
- H. C. Brown Award of the American Chemical Society, 2011.

Nobel Lecture

Introduction

Carbon–carbon bond-formation reactions are important processes in chemistry, because they provide key steps in the building of complex, bioactive molecules developed as medicines and agrochemicals. They are also vital in developing the new generation of ingeniously designed organic materials with novel electronic, optical, or mechanical properties, likely to play a significant role in the burgeoning area of nanotechnology.

During the past 40 years, most important carbon–carbon bond-forming methodologies have involved using transition metals to mediate the reactions in a controlled and selective manner. The palladium-catalyzed cross-coupling reaction between different types of organoboron compounds and various organic electrophiles including halides or triflates in the presence of base provides a powerful and general methodology for the formation of carbon–carbon bonds. The (sp³)C–B compounds (such as aryl- and 1-alkenylboron derivatives) and (sp³)C–B compounds (alkylboron compounds) readily cross-couple with organic electrophiles to give coupled products selectively in high yields. Recently, the (sp)C–B compounds (1-alkynylboron derivatives) have also been observed to react with organic electrophiles to produce the expected cross-coupled products.

Some of representative reactions between various organoboranes and a number of organic electrophiles are shown in Scheme 1. The numbers in parentheses indicate the year they were first reported by our group.

Such coupling reactions offer several advantages:
(1) ready availability of reactants;
(2) mild reaction conditions and high product yields;
(3) water stability;
(4) easy use of the reaction both under aqueous and heterogeneous conditions;
(5) toleration of a broad range of functional groups;
(6) high regio- and stereoselectivity;
(7) insignificant affect of steric hindrance
(8) use of a small amount of catalyst;
(9) application in one-pot synthesis;
(10) nontoxic reaction;
(11) easy separation of inorganic boron compound;
(12) environmentally friendly process.

As one of the defects of the reaction, one would point out the use of bases. However, the difficulty can be overcome by using suitable solvent systems and adequate bases. Consequently, these coupling reactions have been actively utilized not only in academic laboratories but also in industrial processes.

**Coupling Reactions of \( \text{sp}^2 \)C–B Compounds**

**Reactions of Vinylic Boron Compounds with Vinylic Halides**

**Synthesis of Conjugated Alkadienes**

Cross-coupling reactions between vinylic boranes and vinylic halides were not reported to proceed smoothly in the presence of only palladium catalysts. During the initial stage of our exploration, we postulated that a drawback of the coupling is caused by the following aspects of the mechanism. The common mechanism of transition-metal-catalyzed coupling reactions of organometallic compounds with organic halides involves sequential a) oxidative addition, b) transmetalation, and c) reductive elimination.[1] It appeared that one of the major reasons that 1-alkenylboranes cannot react with 1-alkenyl halides is step (b). The transmetalation process between RMX (M = transition metal, X = halogen) and organoboranes does not occur readily because of the weak carbanion character of the organic groups in the organoboranes. To overcome this difficulty we anticipated the use of tetracoordinate organoboron compounds, instead of tricoordinate organoboron derivatives. According to the study by Gropen and Haaland,[2] the methyl group in tetramethylborate was observed to be 5.5 times more electronegative than the methyl group in trimethylborane. Such behavior was also expected for the reaction of triorganoboranes in the presence of base. Thus, we found that the reaction of vinylic boron compounds with vinylic halides proceeds smoothly in the presence of a base and a catalytic amount of a palladium complex to provide the expected conjugated alkadienes and alkenynes stereo- and regioselectively in excellent yields (Table 1).

Although the coupling reaction of \((E)\)-1-alkenylboranes, readily obtained by the hydroboration of appropriate alkyne with disiamylborane or dicyclohexylborane, proceeds readily with \((E)\)- and \((Z)\)-1-alkenyl bromides and iodides to give the corresponding dienes (Table 2), \((Z)\)-1-alkenylboranes, prepared by hydroboration of 1-haloalkynes followed by reaction with tert-butyllithium, gave low product yields, near 50% (Table 3).

Fortunately, it was found that high yields and high stereoselectivity could be achieved by coupling \((Z)\)-1-alkenyl halides with \((Z)\)-1-alkenyldialkoxyboranes, instead of disiamyl- and dicyclohexylborane derivatives (Table 3).[3] Consequently, the cross-coupling reaction of 1-alkenylboranes with 1-alkenyl halides can be achieved readily for the

**Table 1: Cross-coupling reaction of 1 with 2.**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu</td>
<td>BX₂</td>
<td>Ph</td>
</tr>
<tr>
<td>Bu</td>
<td>Ph</td>
<td>Ph</td>
</tr>
</tbody>
</table>

**Table 2: Cross-coupling reaction of \((E)\)-1-vinyldisiamylboranes.**

<table>
<thead>
<tr>
<th>1-Alkenylborane</th>
<th>1-Alkenylbromide</th>
<th>Product</th>
<th>Yield [%] (purity [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu</td>
<td></td>
<td>Ph</td>
<td>86 (98)</td>
</tr>
<tr>
<td>Bu</td>
<td></td>
<td>Hex</td>
<td>88 (99)</td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td>Ph</td>
<td>89 (98)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: \([\text{Pd}(\text{PPh}_3)_4], \text{NaOEt}, \text{benzene}, \text{reflux}, 2 \text{~h.]}\)
The principal features of the cross-coupling reaction are as follows: a) Small catalytic amounts of the palladium complexes (1–3 mol%) are required to obtain the coupled products. b) The coupling reactions are highly regio- and stereoselective and take place while retaining the original configurations of both the starting alkenylboranes and the haloalkenes. The isomeric purity of the products generally exceeds 98%. c) A base is required to carry out a successful coupling. In the initial stage of the study, as mentioned previously, we considered that tetracoordinate organoboron compounds facilitate the transfer of organic groups from the boron to the palladium complex in the transmetalation step. In order to check this possibility, the reaction of lithium (1-hexenyl) methylidisiamylborate was examined, as shown in Equation (1). The coupled product, however, was obtained only in 9% yield. On the other hand, it was found that (trichlorovinyl)palladium(II) complexes 6 and 9, both prepared as pure solids, reacted with vinylborane 7 to give diene 8 [Eqs. (2) and (3)]. In the case of 6, no reaction occurs without a base, whereas the coupling reaction proceeds smoothly in the presence of a base to give the coupled product in 89% yield. The intermediate 9 readily reacts with 7 without a base to provide the same product 8 in almost quantitative yield after 1 h. Consequently, such evidence suggests that vinylic alkoxypalladium(II) compounds such as 9 were necessary intermediates in these cross-coupling reactions. Accordingly, it is considered that the reaction proceeds through the catalytic cycle shown in Scheme 4.[10]

Reactions with Aryl Halides

As described in the previous section, it was discovered that vinylic boron compounds readily react with vinylic halides to give coupled products—conjugated alkadienes.

--

Table 3: Cross-coupling of (Z)-1-hexenyldisiamyl- or (Z)-1-hexenyldiisopropoxyborane.

<table>
<thead>
<tr>
<th>BY₂ in 4</th>
<th>Yield [%] of 5</th>
<th>Purity [%] of 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(Sia)₂</td>
<td>49</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>B(OiPr)₂</td>
<td>87</td>
<td>&gt; 99</td>
</tr>
</tbody>
</table>

Scheme 2. Synthesis of palytoxin.

We next attempted to examine the reaction of 1-alkenylboranes with haloarenes which also have sp²-hybridized carbon–halogen bonds, and found that the reaction takes place smoothly. Representative results are shown in Table 4.

Table 4: Cross-coupling reaction of 10 with iodobenzene.

<table>
<thead>
<tr>
<th>Base</th>
<th>t [h]</th>
<th>Yield [%]</th>
<th>Ratio of 11/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>6</td>
<td>0</td>
<td>100:0</td>
</tr>
<tr>
<td>NaOEt</td>
<td>2</td>
<td>100</td>
<td>100:0</td>
</tr>
<tr>
<td>NaOMe</td>
<td>2</td>
<td>100</td>
<td>100:0</td>
</tr>
<tr>
<td>NaOH</td>
<td>2</td>
<td>100</td>
<td>100:0</td>
</tr>
</tbody>
</table>

This reaction has one more advantage that only one product 11 (head-to-head coupled product) is formed. Additional coupling reactions of vinylic boranes are shown in Table 5. Aromatic bromides and iodides easily react with vinylic boron compounds, but aromatic chlorides do not participate in the coupling, except reactive chlorides, such as allylic and benzylic derivatives. Heteroaromatic halides can also be used as coupling partners. Ortho substituents on the benzene ring do not give difficulty. Thus, the cross-coupling reaction can be used for the synthesis of benzo-fused heteroaromatic compounds [Eq. (4)].

Table 5: Coupling of 1-alkenylboranes with various organic halides.

<table>
<thead>
<tr>
<th>1-Alkenylborane</th>
<th>Halide</th>
<th>Product[a]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu(\equiv)B</td>
<td>PhI</td>
<td>Bu(\equiv)ph</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>PhBr</td>
<td>Bu(\equiv)ph</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>PhCl</td>
<td>Bu(\equiv)ph</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Br-</td>
<td>Bu(\equiv)Br</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>COOEt</td>
<td>Bu(\equiv)COOEt</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Br-</td>
<td>Bu(\equiv)Br</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Cl-</td>
<td>Bu(\equiv)Cl</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>BrC(\equiv)Me</td>
<td>Bu(\equiv)BrC(\equiv)Me</td>
<td>95</td>
</tr>
</tbody>
</table>

[a] Isomeric purity > 98%.

**Aromatic Boron Compounds**

**Reactions with Aromatic Halides**

**Synthesis of Biaryls**

The coupling of aryl halides with copper at very high temperature is called the Ullmann reaction, which is of broad scope and has been used to prepare many symmetrical biaryls. However, when a mixture of two different aryl halides is used, there are three possible biaryl products. Consequently, the development of a selective and general synthesis of all kinds of biaryls has been desired.

The first method to prepare biaryls by the cross-coupling of aryl boranes with haloarenes was reported in 1981 [Eq. (5)]. The reaction proceeds even under heterogeneous conditions to give the corresponding coupled products selectively in high yields. Since this discovery, various modifications have been made to the reaction conditions. As the bases, Na₂CO₃, NaHCO₃, TiCl₃, K₂PO₄, etc. are employed. In some cases, CsF or Bu₄NF can be used instead of the usual bases [Eq. (6)]. Phosphine-based palladium
Catalysts are generally employed since they are stable to prolonged heating; however, extremely high coupling reaction rates can sometimes be achieved by using palladium catalysts without a phosphine ligand, such as Pd(OAc)$_2$, [(η$^5$-C$_5$H$_5$)PdCl]$_2$, and [Pd$_2$(dba)$_3$].

Carbon–carbon bond-forming reactions employing organoboron compounds and organic electrophiles have been recently recognized as powerful tools for the construction of new organic compounds. Among such reactions, aromatic–aromatic (or heteroaromatic) couplings between aromatic boronic acids or esters and aromatic electrophiles to provide symmetrical and unsymmetrical biaryls selectively in high yields have been used most frequently. The importance of biaryl units as components in many kinds of compounds, pharmaceuticals, herbicides, and natural products, as well as engineering materials, such as conducting polymers, molecular wires, and liquid crystals, has attracted enormous interest from the chemical community. Such aromatic–aromatic, aromatic–heteroaromatic, and heteroaromatic–heteroaromatic coupling reaction have been recently reviewed in detail.\[14\]

**Coupling of Aryl Boronic Acid Derivatives Having Highly Sterically Hindered or Electron-Removing Functionalities**

Although steric hindrance of aryl halides is not a major factor in the formation of substituted biaryls, low yields result when ortho-disubstituted aryl boronic acids are used. For example, the reaction with mesitylboronic acid proceeds only slowly because of steric hindrance during the transmetalation to the palladium(II) complex. The reaction of mesitylboronic acids with iodobenzene at 80°C in the present of [Pd(PPh$_3$)$_4$] and various bases has been reported.\[15\] The results are summarized in Table 6.

**Table 6**: Reaction of mesitylboronic acid with iodobenzene under different conditions.

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Yield [%]<strong>[a]</strong></th>
<th>8 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$_2$CO$_3$</td>
<td>benzene/H$_2$O</td>
<td>80</td>
<td>25 (6)</td>
<td>77 (12)</td>
<td>84 (25)</td>
<td></td>
</tr>
<tr>
<td>Na$_2$CO$_3$</td>
<td>DME/H$_2$O</td>
<td>80</td>
<td>50 (1)</td>
<td>66 (2)</td>
<td>83 (7)</td>
<td></td>
</tr>
<tr>
<td>K$_3$PO$_4$</td>
<td>DME/H$_2$O</td>
<td>80</td>
<td>70 (0)</td>
<td>95 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaOH</td>
<td>DME/H$_2$O</td>
<td>80</td>
<td>95 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ba(OH)$_2$</td>
<td>DME/H$_2$O</td>
<td>80</td>
<td>99 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] GLC yields of the coupling product based on iodobenzene; the yields of mesitylene are shown in parentheses.

Aqueous Na$_2$CO$_3$ in benzene or DME (dimethoxyethane) is not effective as a base for the coupling of mesitylboronic acid and the reaction is not completed even after two days. Although the side reactions such as homocoupling are negligibly small, the formation of mesitylene by hydrolytic deboronation was observed, increasing with the reaction time. It is noteworthy that such hydrolytic deboronation is faster in benzene/H$_2$O than in the modified conditions of aqueous DME. On the other hand, the addition of stronger bases, e.g., aqueous NaOH or Ba(OH)$_2$, both in benzene and DME, exerts a remarkable effect on the acceleration rate of the coupling. By using aqueous Ba(OH)$_2$ in DME at 80°C, mesitylboronic acid couples with iodobenzene within 4 h to give the corresponding biaryl in a quantitative yield. Some such coupling reactions are depicted in Equations (7) and (8).

**An alternative procedure**, using the esters of boronic acids and anhydrous base, has been developed for sterically hindered aryl boronic acids and provide high yields. The coupling can be readily achieved by using the trimethylene glycol ester of mesitylboronic acid and Cs$_2$CO$_3$ or K$_3$PO$_4$ in DMF at 100°C to give a quantitative yield of the coupled products [Eq. (9)]\[15\].

![Equation (7)](image)

![Equation (8)](image)

![Equation (9)](image)

Even without sterically hindered substrates, the reaction under aqueous conditions is often undesirable because of competitive hydrolytic deboronation. A kinetic study\[16\] into the reaction of substituted aryl boronic acids showed that electron-withdrawing substituents accelerate the deboronation. Although there is no large difference between meta- and para-substituted phenylboronic acids, substituents at the ortho position may greatly increase the rate of deboronation. For example, a 2-formyl group on aryl boronic acids is known to accelerate the rate of hydrolytic deboronation.\[16\] Indeed, the coupling of 2-formylphenylboronic acid with 2-iodotoluene at 80°C using Na$_2$CO$_3$ in DME/H$_2$O gives only a 54% yield of the corresponding biaryl, with accompanying benzaldehyde (39%). Aprotic conditions are desirable for such boronic acids that are sensitive to aqueous base. Thus, the trimethylene glycol ester of 2-formylphenylboronic acid
readily couples with iodobenzene at 100°C in DMF to give the coupled product in a yield of 89%, with less than 10% benzaldehyde formed [Eq. (10)].\(^{[15]}\)

Recently, Buchwald et al. reported interesting catalysts and ligands for the preparation of tetra-ortho-substituted unsymmetrical biaryls.\(^{[17]}\) Among the biphenyl-based ligands tested, 14 gave excellent results, whereas significant amounts of aryl bromide reduction were observed when the ligands 13 were used (Table 7).

### Table 7: Ligand effects in the coupling of hindered substrates.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conv [%]</th>
<th>Biaryl [%]</th>
<th>Biaryl/ArH</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>47</td>
<td>33</td>
<td>2.3</td>
</tr>
<tr>
<td>13b</td>
<td>20</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>13c</td>
<td>74</td>
<td>40</td>
<td>1.9</td>
</tr>
<tr>
<td>14</td>
<td>100</td>
<td>91</td>
<td>10</td>
</tr>
</tbody>
</table>

**Coupling with Aromatic Chlorides**

In aromatic–aromatic cross-coupling reactions, cheap and readily accessible aryl chlorides are particularly important from an industrial viewpoint as starting materials. Recently some research groups, especially Fu’s group\(^{[18]}\) and Buchwald’s group\(^{[19]}\) have reported very efficient methods for the reaction of aryl chlorides. For example, Fu and co-workers\(^{[18]}\) have observed that the use of \([\text{Pd}_2(\text{dba})_3]/\text{PPh}_3\) as the catalyst and ligand result in a wide range of aryl and vinyl halides, including chlorides, undergoing Suzuki cross-coupling with aryl boronic acids in very good yields, typically at room temperature (Table 8). Furthermore, these catalysts display novel reactivity patterns, such as the selective coupling in the presence of \([\text{Pd}_2(\text{dba})_3]/\text{PCy}_3\)/KF of a sterically hindered aromatic chloride [Eq. (11)].

Despite the generally good yields in many Suzuki reactions of chloroarenes, comparatively large amounts of catalyst are required. Beller et al. reported a new catalyst system, with which they achieved the coupling of non-activated and deactivated aryl chlorides highly efficiently in good yields with generally only 0.005 mol% palladium, and thus under the industrially allowed level.\(^{[20]}\) For instance, as a new efficient catalyst system, they used diadamantyl-n-butyolphosphane (BuPAd

### Applications in the Synthesis of Biaryls

The anti-HIV alkaloids michellamine A (17) and B (18) have been synthesized. The tetraaryl skeleton of the michellamines was constructed by formation, first, of the inner (nonstereogenic) biaryl axis and subsequently of the two other (stereogenic) axes by using a double Suzuki-type cross-coupling reaction between the dinaphthalene ditriflate 15 and isoquinolineboronic acid 16 [Eq. (13)].\(^{[21]}\)

The discovery and development of penicillin and other antibacterial agents as drugs to fight infectious diseases were milestone victories of humankind over bacteria. While these agents saved millions of lives, they did not tame bacteria. On the contrary, this war led to the emergence of newer and more-dangerous bacterial strains that responded defiantly against known antibacterial agents. Vancomycin is a member of the polycyclic glycopeptide class of antibiotics and has proved to be the last line of defense against drug-resistant bacteria. The daunting synthetic challenge posed by its structure is largely due to the strained nature of the 12-membered biaryl framework (AB ring system) and the two 16-membered biaryl ethers (COD and COE ring systems).
Nicolaou and his group reported a Suzuki coupling approach to the AB-COD bicyclic system of vancomycin.\[22\] Suzuki coupling of iodide 19 with 20 was facilitated by a [Pd(Ph₃)₄] catalyst and Na₂CO₃ to give a 1:1 mixture of the two atropisomers 21a and 21b in 80% combined yield [Eq. (14)]. The coupling of the parent boronic acid corresponding to 20 (without methyl groups) with iodide 19 led to a single compound. Thereafter, the total synthesis of the vancomycin aglycon was reported by the same workers.\[23\]

The novel compound tetrakis(phenothiazinylphenyl)methane (23), showing remarkably large Stokes shift and a reversible low oxidation potential, can be prepared in a good yield by Suzuki coupling of tetrakis(p-bromophenyl)methane \[22; \text{Eq. (15)}\].\[24\]

Oligothiophene-functionalized 9,9-spirobifluorene derivatives have been synthesized in high yields by Suzuki coupling. The Negishi coupling reaction between oligothiophenylzinc chloride and various 9,9-spirobifluorene bromides with [Pd(PPh₃)₄] as the catalyst successfully produce the desired compounds. However, the Negishi coupling provided low yields, compared to the Suzuki coupling [Eq. (16)].\[25\]

**Solid-Phase Synthesis (Combinatorial Methodology)**

Solid-phase reactions play an important role in parallel synthesis and combinatorial chemistry, particularly in the area of medicinal chemistry, where their potential has emerged as a result of the possibility of automation. A considerable amount of attention has been focused on adapting and exploiting the advantage of solid-phase synthesis (SPS) for the production of libraries of such organic compounds. In this context, transition-metal-promoted reactions serve as efficient methods because they proceed under mild conditions and are compatible with many functional groups. For instance, solid-phase Suzuki coupling has largely been developed by the reaction of a resin-bound aryl halide with solution-phase boronic acids.\[14\] Recently, the viability of solid-supported boronic acids as reagents for Suzuki couplings was successfully demonstrated.\[26\]

**Applications in Polymer Chemistry**

Aromatic, rigid-rod polymers play an important role in a number of diverse technologies including high-performance engineering materials, conducting polymers, and nonlinear optical materials. The Suzuki polycondensation (SPC) reac-
tion of aryl diboronic acids and dihaloarenes for the synthesis of poly(p-phenylenes) was first reported by Schlüter et al.\[27\] SPC is a step-growth polymerization of bifunctional aromatic monomers to poly(arene)s and related polymers (Scheme 5).\[28\] The required functional groups—boronic acids or esters on one side, and bromide, iodide, and so forth on the other—may be present in different monomers (AA/BB approach) or combined in the same monomer (AB approach).

**AA/BB approach**

\[
\text{(RO)₂B}^+\text{Ar}^-\text{B(OR)}₂ + X^-\text{Ar}^-\text{X} \xrightarrow{\text{[Pd]}} \text{Ar}^-\text{Ar}^-\text{X}\]

**AB approach**

\[
X^-\text{Ar}^-\text{B(OR)}₂ \xrightarrow{\text{[Pd]}} \text{Ar}^-\text{Ar}^-\text{X}\]

*Scheme 5.* Graphical representation of the Suzuki polycondensation

The method was extensively applied to monodisperse aromatic dendrimers, water-soluble poly(p-phenylene), planar poly(p-phenylenes) with fixed ketoimine bonds, poly(phenylenes) fused with polycyclic aromatics, and nonlinear optical materials.\[14\] One such application is shown in Equation (17).\[29\]

**Coupling Reactions of (sp³)C–B Compounds**

Although organometallic reagents with 1-alkenyl, 1-alkynyl, and aryl groups were successfully used for the coupling reactions, those with alkyl groups having sp³ carbons with β hydrogens were severely limited due to the competitive side reactions. In 1971–1972 Kochi, Kumada, and Corriu reported independently that the reaction of alkyl Grignard reagents with alkenyl or aryl halides are markedly catalyzed by FeIII or NiII complexes, and then Negishi demonstrated the synthetic utility of alkyl zinc compounds by the use of a palladium catalyst. Thereafter, alkyl lithium, tin, and aluminum reagents were also employed for such cross-coupling reactions. The reaction of alkyl borane derivatives is particularly useful when one wishes to start from alkenes via hydroboration. Consequently, we intended to examine the coupling reactions between alkyl boron compounds and various organic halides in the presence of a base and a palladium complex, and found that no cross-coupling reactions of B-alkyl-9-borabicyclo[3.3.1]nonanes (B-R-9-BBN), readily obtainable from alkenes by hydroboration, with 1-halo-1-alkenes or haloarenes occurred under the standard coupling conditions using [Pd(PPh₃)₄] as a catalyst, but the coupling proceeds smoothly by using a catalytic amount of [PdCl₂(dppf)] and bases, such as NaOH, K₂CO₃, and K₃PO₄ to give the corresponding substituted alkenes or arenes in excellent yields [Eq. (18)].\[30,31\] Because the reaction is tolerant of a variety of functionalities on either coupling partner, stereochemically pure functionalized alkenes and arenes can be obtained under mild conditions [Eq. (19)]. The utility of the reaction was demonstrated by the stereoselective synthesis of 1,5-alkadienes (26) [Eq. (20)] and the extension of a side chain in steroid 27 [Eq. (21)].\[30,31\]

Many chemists applied such a Suzuki coupling reaction by using B-saturated alkylboron compounds. For instance, Danishefsky et al. reported a total synthesis of the promising anticancer agent (−)-epothilone B by using the coupling method [Eq. (22)],\[32,33\] and a sister compound, epothilone A, was also synthesized by a similar procedure.\[34\] A full paper
describing the total synthesis of epothilones A and B has appeared more recently.[35]

Marine polyether toxins present challenging synthetic targets because of their structural complexity and exceptionally potent biological activities. The most critical issue in the synthesis of these large polyether compounds is the development of synthetic methods for the convergent coupling of polyether fragments. Despite recent advantages in the synthesis of medium-sized cyclic ethers, only a few methodologies for the convergent assembly of six-membered polyether structures were reported. A new strategy for the synthesis of trans-fused polyethers based on the palladium(0)-catalyzed Suzuki coupling reaction of alkyl boranes with cyclic enol triflates has been developed by Tachibana et al.[36] As shown in Equation (23), the cross-coupling reaction is carried out in the presence of cesium carbonate as a base and triphenylarsine as a co-ligand in DMF at room temperature. Further reactions give the expected trans-fused polyether.

**Base Problems**

In cross-coupling reactions of organoboron compounds, the presence of a base is essential; no reaction occurs without base. On the other hand, there are many organic compounds that are sensitive to bases. Consequently, the careful use of bases is required in such cases. For example, Table 9 shows that the selection of a base and solvent system provides markedly different yields of the coupled products. By careful selection of the reaction conditions (e.g., [PdCl2(dpff)]/K2CO3/DMF), high yields of the desired coupled products can be achieved [Eq. (24) and (25)].

| Table 9: Solvent and base effects on the cross-coupling reaction.[a] |
|---|---|---|---|---|
| Solvent | Base (equiv) | T [°C] | t [h] | Yield [%] |
| DMF | KOAc (4) | 50 | 18 | 18 |
| DMF | K2CO3 (2) | 50 | 18 | 64 |
| CH3CN | K2CO3 (4) | 50 | 18 | 46 |
| DMF | K3PO4 (4) | 50 | 20 | 92 |

[a] Catalyst: [PdCl2(dpff)].
Coupling Reactions of (sp)C–B Compounds

Alkynylboranes have long been known to be useful synthetic intermediates. Compared to other organoboranes, they are easily hydrolyzed by base. Because of this property, alkynylboron compounds have not been employed in the Suzuki coupling reaction, in which the presence of bases is essential. Recently, Soderquist et al. have found that the addition of B-methoxy-9-borabicyclo[3.3.1]nonane to alkynyllithium reagents gives stable complexes 29, which undergo efficient Suzuki coupling to produce a variety of alkynyl derivatives 30 [Eq. (26), Table 10].

Almost at the same time, Fürstner and Seidel reported the same reaction. The necessary alkynyl borates in the palladium-catalyzed C–C bond formation are prepared from 9-methoxy-9-BBN and a polar organometallic reagent RM, such as 1-alkynylsodium, -potassium, and -lithium compounds, and not as usual from boranes and bases. This approach allows cross-couplings of organic halides with, for example, alkynyl, methyl, or TMSCH₂ groups. The method is highly chemoselective and turned out to be compatible with aldehyde, amide, ketone, ester, and cyano functions as well as with basic nitrogen atoms in the substrates. Some of the results are shown in Table 11. This reaction has been used to prepare compound 31, which is highly valuable for its chemoluminescence properties.

Most recently the palladium-catalyzed cross-coupling reaction of potassium alkynyltrifluoroborates with aryl halides or triflates has been reported to give readily coupled products. The potassium alkynyltrifluoroborates are air- and moisture-stable crystalline solids that can be stored indef-

Table 10: Coupled products from 29 [see Eq. (26)].

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>nBu</td>
<td>C₆H₅</td>
<td>60 (92)</td>
</tr>
<tr>
<td>SiMe₃</td>
<td>C₆H₅</td>
<td>64</td>
</tr>
<tr>
<td>Ph</td>
<td>C₆H₅</td>
<td>94</td>
</tr>
<tr>
<td>nBu</td>
<td>p-MeOC₆H₄</td>
<td>62 (68)</td>
</tr>
<tr>
<td>SiMe₃</td>
<td>CH₂=CC₆H₅</td>
<td>88</td>
</tr>
<tr>
<td>tBu</td>
<td>cis-CH=CH-tBu</td>
<td>56</td>
</tr>
<tr>
<td>SiMe₃</td>
<td>trans-CH=CH-nBu</td>
<td>55</td>
</tr>
</tbody>
</table>

[a] Yields of isolated analytically pure compounds (GC yields).

The Future

Today, the Suzuki reaction continues to evolve, with many new possibilities reported during the past decade. For example, solid-phase Suzuki coupling has been developed by using either resin-bound aryl halides with solution-phase boronic acids or vice versa. Such approaches, of course, play an important role in the combinatorial and parallel methodologies now used to explore chemical reactivity, and is especially well-suited to medicinal chemistry.

Increasingly, industry is seeking to use more environmentally friendly processes. These often require ingenious solutions to which Suzuki coupling is well-suited. Research groups around the world are investigating modifications of the reaction that work in aqueous media or with trace amounts of catalysts. For example, Leadbeater and his team carry out Suzuki coupling using an ultralow (ppb) palladium concentration in water, while Kabalka and colleagues have combined a solvent-free, solid-state approach with the application of microwave radiation to achieve coupling in just a few minutes. Ionic liquids, which are excellent solvents for transition-metal catalysts, are also being investigated.

We can expect to see many more interesting versions of the Suzuki coupling in the future.

Table 11: Pd-catalyzed arylation of alkynylmetal reagents mediated by 9-MeO-9-BBN derivatives.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>RM</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-bromobenzo-phenone</td>
<td>MeC≡</td>
<td>COPh</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>CNa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-bromobenzaldehyde</td>
<td>PhCl</td>
<td>CHO</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>CNa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethyl 4-bromobenzozoate</td>
<td>MeC≡</td>
<td>CO₂Et</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>CNa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-bromobenzonitrile</td>
<td>PhCl</td>
<td>CN</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>CNa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9,10-dibromanthracene</td>
<td>Ph≡Cl</td>
<td>PhPh</td>
<td>84</td>
</tr>
</tbody>
</table>

[29]
I would like to acknowledge the late Professor Herbert C. Brown for his cordial encouragement and warm guidance to me, not only in chemistry but also my life. Thanks are also due to many former co-workers, including graduate and undergraduate students at Hokkaido University.

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[31] Palladium-Catalyzed Inter- and Intramolecular Cross-Coupling Reactions of B-alkyl-9-borabicyclo[3.3.1]nonane Derivatives with 1-Halo-1-alkenes or Haloarenes. Syntheses of functional-


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