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Asymmetric Catalysis

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Facts are the Enemy of Truth—Reflections on Serendipitous Discovery and Unforeseen Developments in Asymmetric Catalysis

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1. Prologue

The title of this Essay, "Facts are the Enemy of Truth", which is a line spoken by Don Quixote, reflects my view after 50 years of study in chemistry. In various scientific fields, researchers unearth a broad range of facts, yet most of these are far from the truth. Many findings and postulates are not universally true because they are rooted in very limited conditions, while in reality the scientific universe is limitless. A large body of facts approaches the truth only when it is systematically and thoughtfully arranged.

However, if scientists are careful arrangers of facts, they are also sometimes the mediums of inspiration. Uncertainty is the cornerstone of science and, in fact, great scientific discoveries are not exclusively the result of careful logical progression. Many marvelous discoveries have been made while researchers, often young and inexperienced, were looking for something else. Talented scientists have a special ability to capture unexpected good fortune, and this is what is called "serendipity."[1]

I am proud of having been a chemist, because we not only make observations on the natural world, but also create and produce values. Our science is beautiful, exciting, and often beneficial for humankind. Simply stated, chemistry is a science of substances and materials and possesses infinite possibilities. Chemists attempt to understand the substances and materials in all natural phenomena on the atomic and molecular levels. Chemistry is also a science that can create at will new matter with desired properties and functions. This means that we can produce all kinds of needed objects by using our accumulated knowledge. Science is crucial for sustaining our species, because Mother Nature is unable to provide all the needs of society.

Chirality or handedness is an intrinsic feature in science, technology, and even society.[2] Many organic compounds have a right and left form, known as enantiomers, which possess identical free energy and diverge from each other only slightly. However, this difference can become very large in biological, living organisms. We know, for example, that the occurrence of enantiomers causes things to taste and smell differently. Such a structural difference can become even more serious in the administration of synthetic drugs.[3] A typical example is Darvon, which is a painkiller. Its mirror image is Novrad, which acts as an antitussive (anticough) agent.

The phenomenon of chirality occurs in biological systems because the receptors in our bodies are mostly proteins made up of only *S*-configured amino acids. Certain small organic molecules are bound reversibly to the binding sites such as enzymes through various weak interactions, thereby prohibiting or promoting their biological actions. In order to form such a precise molecular complex, the structures of the small and large molecules must be complementary, both electronically and spatially. Thus, such biologically active compounds must have an appropriate surface potential that is generated from the existence of oxygen or nitrogen functionalities. Importantly, the presence of a defined *R* or *S* stereogenic center(s) makes the chiral molecules single-handed. Life thus depends on molecular chirality.

Scientists face a multitude of options when choosing their field of research, but molecular chirality quickly became my major focus. My academic career has been a challenge to Louis Pasteur, who stated in 1851 when he was 29 years old, "Dissymmetry is the only and distinct boundary between biological and nonbiological chemistry. Symmetrical physical or chemical force cannot generate molecular dissymmetry." Rigorously speaking, this is not true, but was accepted as valid from a practical point of view until just 40 years ago.

2. The Birth of Organometallic Asymmetric Catalysis

A generally reliable chemical method is needed for the production of enantiomerically pure organic compounds. The practical means, however, were not available until relatively recently. For preparative purposes, in addition to the classical resolution of racemates, chemists had long used various

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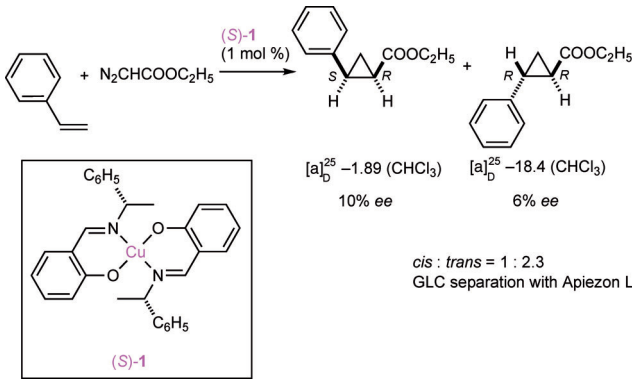
synthetic methods, including transformation of naturally occurring chiral compounds and stereoselective reactions based on intramolecular or intermolecular chirality transfer. These are not always satisfactory.

The progress of science is totally unpredictable. A principle for solving this fundamental chemical problem was discovered in 1966 by Professor Hitosi Nazaki's group at Kyoto University, where I was a 27-year-old instructor. As illustrated in Scheme 1, the reaction of styrene and ethyl



Scheme 1. The first example of asymmetric catalysis using a chiral organometallic complex.

diazoacetate at 58–60 °C in the presence of a 0.01 molar equivalent of an optically active Schiff base/Cu^{II} complex **1** gave nonracemic cyclopropane products with 6–10 % enanatiomeric excess (*ee*) and in 72 % yield.[4] This asymmetric cyclopropanation, albeit with a low enantioselectivity, provided the general principle of asymmetric catalysis that is now widely used in research and industry (Figure 1).[5–7] As so often happens, however, this "science in action" totally differed from the story of the resulting technology and innovation. This serendipitous finding was later developed to useful technologies that were completely unforeseen by its discoverers; they gained answers to questions that they were not even asking. In fact, this discovery resulted not from a particular synthetic purpose. Rather, it came by accident, from our mechanistic curiosity.

In the 1960s, organic chemistry of reactive intermediates such as carbocations, free radicals, and carbanions, was in full bloom. Back then, we were intrigued by the behavior of carbene intermediates generated from diazoalkanes by photolysis or thermolysis with and without transition metals. Since the postulate by Hertzberg and Shoosmith in 1959,[8] the relation between the structure, spin multiplicity, and reaction modes of carbenes was a most fascinating subject. Singlet CH_2 with a bent σ^2 structure (first excited state) and triplet CH_2 with a less bent σ^1p^1 structure (ground state) are interconvertible by intersystem crossing. Singlet carbenes are known to undergo stereospecific cis cycloaddition to olefins, with retention of configuration, but also randomly insert into C–H linkages, while the triplet species add to olefinic linkages in a stepwise, nonstereospecific fashion and react with C–H bonds by a radical mechanism. Thus both singlet and triplet behave nonselectively, though in different manners. Notably,

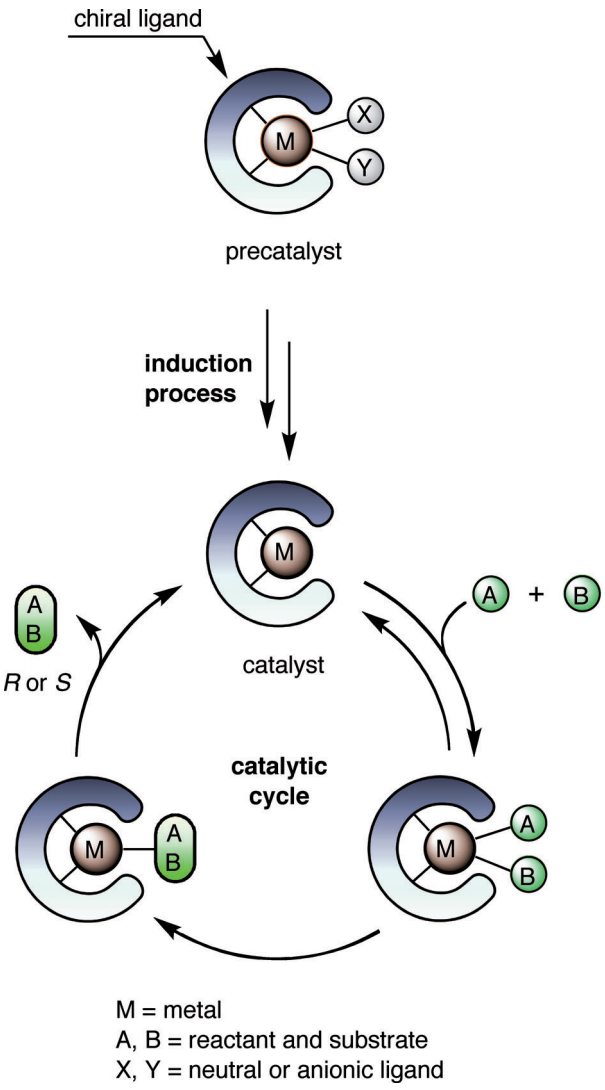


Figure 1. The general principle of asymmetric catalysis.

transition metals, particularly Cu powder, oxides, or salts, catalyze the decomposition of diazoalkanes, resulting in highly selective carbene reactions, namely, stereospecific cyclopropanation without C–H insertion. The role of the transition metals was still unclear. Earlier in 1952, Yates noted that reaction of α-diazoketones and alcohols in the presence of Cu powder gave only α-alkoxy ketone products resulting from carbene O–H insertion, instead of esters by the Wolff rearrangement, and proposed the formation of an α-ketocarbene intermediate bound to the Cu surface with the valence electrons completing the octet of the carbenic carbon atom.[9] This sensible explanation was followed by many publications claiming the reactive species had a carbene/Cu bond.[10] Hammond, however, postulated the possibility of the intervention of a charge-transfer complex between triplet CH_2 and Cu powder or soluble Fe^{III} tris(dipivaloylmethide).[11] He considered that the delivery of the CH_2 fragment to an olefin occurs through a triplet 1,3-biradical but, as inferred from George Porter's finding of rapid quenching of anthracene phosphorescence by Fe salts,[12] its spin conversion

to the singlet state could be instantaneous in the field of the paramagnetic heavy metals, resulting in the stereospecific cyclopropanation without C–H insertion. This interpretation was also reasonable.

Since a "chiral molecular cause" must kinetically reflect the "chiral consequence", we wanted to chemically confirm the existence of the carbene species covalently bound to the Cu atom. Thus we hit upon the idea that an optically active Cu molecular catalyst serves as a diagnostic tool for the hypothesis. Asymmetric induction, if observed in the olefin cyclopropanation with (*S*)-**1** (Scheme 1), would provide definite evidence for the intervention of a carbene/Cu intermediate. This was our scientific logic. At the time, because a polarimeter with a 5 cm quartz cell was the only instrument to determine enantiomer composition, the pure *cis*- and *trans*-cyclopropanecarboxylic esters had to be collected in quantities of around 100 mg by repeated preparative GLC separation. This needed laborious overnight work. And we were delighted to know that, as we anticipated, the products were definitely nonracemic.[4] The optical purities and absolute configurations were determined after converting to the carboxylic acids and by comparison of the signs and values of the optical rotation with reported data (dextro- or levorotatory).[13] Similar asymmetric induction was seen in the reaction of diazomethane and *trans*-1-phenylpropene catalyzed by (*S*)-**1**, giving (1*R*,2*R*)-*trans*-1-methyl-2-phenylcyclopropane in 8% *ee*. Likewise, in place of the soluble chelate complex **1**, solid copper(II) tartrate could also be used as a chiral catalyst, but less effectively.

The concept of "molecular catalysis" utilizing structural and electronic characteristics of coordination complexes had not yet emerged in the 1960s. Catalysts were classified merely by their solubility in reaction media, heterogeneous versus homogeneous. Metal carbonyl complexes for the Reppe reaction were a typical example of the latter.

It is now well recognized that asymmetric catalysis is achievable by the use a molecular catalyst consisting of a metallic element and chiral organic ligand(s). As illustrated in Figure 1, the active metal center generates catalytic reactivity, accelerating the reaction repeatedly, while the attending chiral ligand controls stereoselectivity in the absolute sense. First, the metallic center accommodates molecules A and B, or one of these. The activated molecules react to form a new molecule A–B, which dissociates from the metal to give free A–B and the original catalyst. This cycle is repeated many times until A or B is fully consumed. Here, if the chiral catalyst is well designed, the reaction is not only accelerated but produces a chiral compound favoring either a right- or left-handed enantiomer. As such, a compact organometallic catalyst with a molecular weight of less than 1000 (or 20 Å in length) defines the stereochemical outcome in an absolute sense and provides an ideal means for multiplication of the molecular chirality. The periodic table contains many catalytic metals, while the permutation of chiral organic ligands is unlimited. Precise chemical synthesis requires a wide variety of asymmetric reactions, and only the concept of "molecular catalysis" can cope with this requirement. In fact, recent progress of asymmetric catalysis along this line entirely changed the synthetic procedures in research laboratories and industry for pharmaceuticals, agrochemicals, flavors, and fragrances.[6]

The asymmetric cyclopropanation carried out in 1966 is unforgettable. We were thrilled with the finding at the time. However, no one appreciated its significance, because this reaction was practically meaningless. First, the enantioselectivity was up to only 55:45 or 53:47, slightly favoring one enantiomer over the other, and secondly the three-membered-ring-forming reaction was a bit peculiar, and not generally useful. Therefore *The Journal of the American Chemical Society* rejected our manuscript, which we ended up publishing in *Tetrahedron Letters*.[4a] This early effort, though unappreciated for a long time, was eventually one of the reasons for the 2001 Wolf Prize in Chemistry to be given to myself together with Henri B. Kagan and K. Barry Sharpless. Two years later, in 1968, I moved from Kyoto to Nagoya, where I no longer worked on this interesting but seemingly useless subject.

Measurement is the mother of science. As seen above, research into asymmetric synthesis relies heavily on methods for determining the enantiomeric purity of nonracemic compounds (optical purity or enantiomeric excess). Until the late 1970s, chemists had long used a polarimeter for this purpose, but access to the requisite analytically pure sample remained difficult. Then, synthetic chemists begun to determine the optical purity by using ^{1}H NMR (60 to 100 MHz) with chiral lanthanide shift reagents, or more conveniently, after derivatization by a chiral auxiliary, giving a diastereomeric mixture. For example, chiral alcohols were converted to the Mosher's α-methoxy-α-trifluoromethyl-α-phenylacetic (MTPA) esters or 1-(1-naphthyl)ethylcarbamates; carboxylic acids were converted to 1-(1-naphthyl)ethyl amides; and amines were condensed with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl isothiocyanate (GITC). Chiral GLC columns were also used for certain volatile compounds. Later, development of HPLC techniques as well as ^{19}F and high-field ^{1}H NMR significantly facilitated the analysis of the diastereomeric compounds. It was only in the late 1980s that HPLC utilizing a polysaccharide-based chiral stationary phase became available and thus allowed the direct analysis of UV-active chiral compounds without derivatization. Lack of such useful analytical methods had long hampered the progress of asymmetric synthesis.

3. Turning to Asymmetric Hydrogenation

Later, I became interested in asymmetric hydrogenation (AH), because this subject is fundamental and less esoteric than the asymmetric cyclopropanation. This reaction provides the most powerful way to produce a wide array of enantioenriched compounds in a large quantity without producing any waste. Unlike conventional metal-based reducing agents, hydrogen gas is inexpensive and clean. AH has enormous potential from both a scientific and technological point of view, if one can find an efficient catalyst. Although the H–H bond can be cleaved by various transition-metal complexes, it is not easy to find a truly efficient catalyst showing a high turnover number and a high turnover frequency. In 2001, I

had the honor to share the Nobel Prize in Chemistry[14] with William S. Knowles[15] for the achievement of AH, and with K. Barry Sharpless[16] for his work on asymmetric oxidation.

What stimulated me to get involved in hydrogenation chemistry? My interest in hydrogenation stemmed largely from my postdoctoral stay at Harvard University with E. J. Corey from 1969 to 1970, where my research theme was the synthesis of prostaglandins. Corey asked me to hydrogenate one of the two olefinic bonds in the $PGF_{2\alpha}$ derivative to the $PGF_{1\alpha}$ form with only one double bond. Although the final solution to saturate the cis double bond was obtained by using a simple heterogeneous Pd/C catalyst,[17] I tested many kinds of homogeneous systems as well. I often discussed this topic with John A. Osborn, an assistant professor and a former student of Geoffrey Wilkinson of Imperial College, London, who developed hydrogenation catalyzed by a phosphine/Rh complex.[18]

The 14-month stay at Harvard inspired me to further explore the fascinating AH subject at Nagoya, because this area was closely tied in with our original Cu-catalyzed asymmetric cyclopropanation.[4] Furthermore, all Japanese chemists were aware of Akabori's pioneering (though not synthetically effective) 1956 work on heterogeneous AH of oximes and oxazolones catalyzed by metallic Pd drawn on silk.[19] These events stimulated me to study AH. However, I already had a range of significant research subjects lined up in my laboratory and, because of its limited capacity, was unable to immediately start this important research.

Historically, AH of prochiral olefins with chiral phosphine/Rh^I catalysts began in 1968, although saturated products with only 3–15% *ee* were produced.[20] When I came to this field, Kagan had already succeeded in AH of a protected dehydroamino acid catalyzed by a DIOP/Rh complex forming phenylalanine in approximately 80% *ee*, then recorded as 72% *ee*.[21] Furthermore, a group led by Knowles at Monsanto established the industrial synthesis of the antiparkinsonian drug L-DOPA using a similar AH with a DIPAMP/Rh catalyst.[15,22] Consequently, AH chemistry was considered already complete with no significant problems remaining to be solved. Obviously this was not true at all. The real fact was that certain amino acids were synthesized by chiral Rh-catalyzed AH. This was just a starting point for creating a significant scientific/technological field.

The aim of my research group at Nagoya was to develop a generally applicable catalytic system. We wanted to invent a BINAP/Rh^I catalyst (BINAP = 2,2′-bis(diphenylphosphino)1,1′-binaphthyl) with an atropisomeric C_2 chiral architecture, because the molecular model, as shown in Figure 2, indicates that first/third and second/fourth quadrants are spatially well differentiated because of the presence of four axially and equatorially oriented *P*-phenyl rings. However, the synthesis of pure (*R*)- or (*S*)-BINAP was unexpectedly difficult. We started this work in 1974 with the late Hidemasa Takaya, a long-term collaborator of mine, and continued for six years before we achieved this initial goal.[23] Numerous groups in Japan and abroad tried to synthesize the desired BINAP ligand without success, because the standard chemistry did not work at all. We planned to synthesize an enantiomeric BINAP starting from optically pure 2,2′-diamino-1,1′-binaphthyl. Unfortunately, all our attempts were disappointingly irreproducible or, in most cases, resulted in formation of a racemic intermediate or final diphosphine product.[24] We remained patient, however, and, finally, managed to resolve racemic BINAP with an optically active amine/Pd complex.

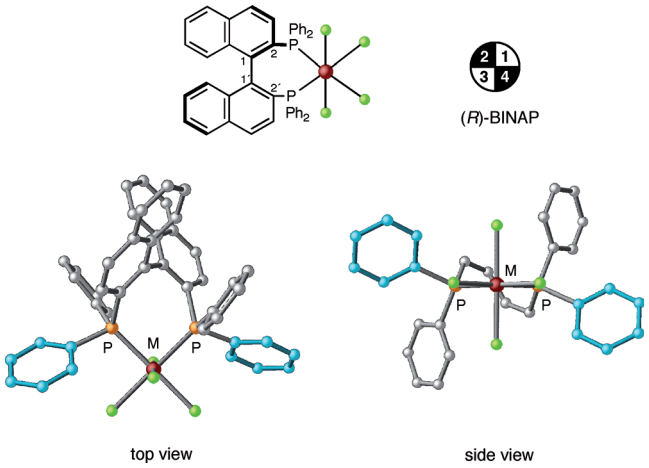
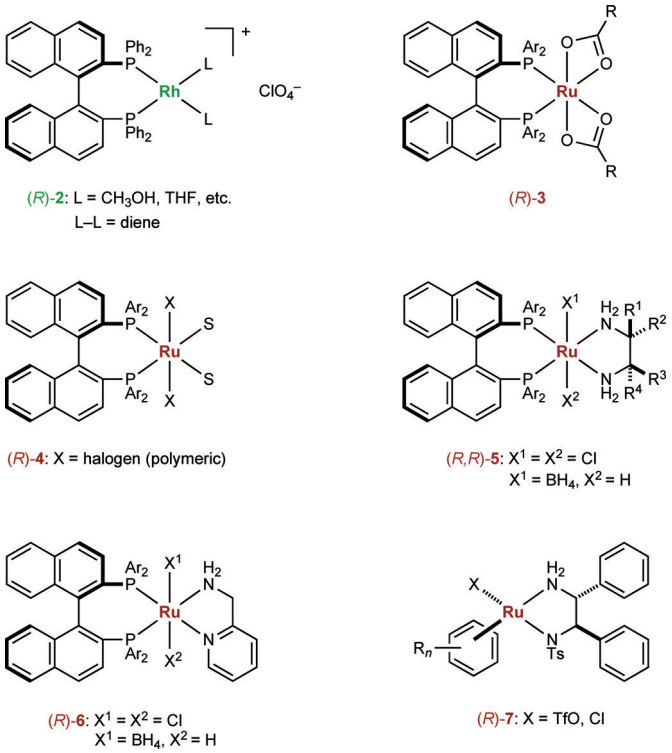


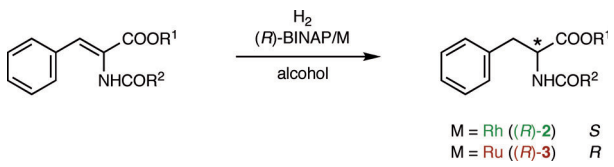
Figure 2. Chiral environment of an (*R*)-BINAP/transition-metal complex. The second and fourth quadrants are more crowded than the first and third quadrants. For clarity, naphthalene rings are omitted in the side view.

Eventually, in 1980, the (*R*)- and (*S*)-BINAP/Rh complexes ((*R*)- and (*S*)-2; Figure 2 and Scheme 2) became publically known.[23] We were able to publish a paper on the synthesis and use of the BINAP ligand for AH of N-protected



Scheme 2. Chiral transition-metal complexes for asymmetric hydrogenation.

dehydro amino acids (Scheme 3). For example, the reaction of the olefinic substrate ($R^1 = H$, $R^2 = C_6H_5$) was achieved in ethanol using (*R*)-2 (L = CH_3OH) with a substrate/catalyst molar ratio of 100 under 4 atm of H_2 and at room temperature, giving the amino acid in 97% yield. The *S* enantioselectivity, still judged from the optical rotation of the product, was almost perfect.



Scheme 3. Asymmetric hydrogenation of dehydroamino acids.

BINAP later grew to become one of the key players in the field of asymmetric catalysis, but the progress was not straightforward. In 1978, two years before the scientific publication, we asked the Ajinomoto Company to submit a patent application for chiral BINAP/Rh catalyst **2** on our behalf.[25] This Japanese company had widely commercialized monosodium (*S*)-glutamate, an "umami" taste enhancer, and other amino acids, and had a long tradition of excellent fermentation technology. Therefore, its researchers were all faithful followers of Pasteur and were not convinced that artificial asymmetric catalysts could be superior to microorganisms using enzymes. It was understandable that they undervalued the potential of our chemical asymmetric synthesis. But there are scientific advances and technological developments that even the best professionals cannot predict. This is the very nature of science and technology.

In fact, the BINAP/Rh chemistry failed to take us to our desired goal. In the late 1970s and early 1980s, it was generally considered that Rh^I was the best metal for AH, based on the many successful asymmetric syntheses of amino acids. This was not true, however. Ironically, the invention of the cationic BINAP/Rh complex **2** was the start of our long struggle with AH. This complex shows outstanding chiral recognition abilities, as expected from Figure 2.[26] However, this is merely a static characteristic. The nice molecular shape is not enough, because asymmetric catalysis is four-dimensional (4D) chemistry.[5] The efficiency can only be achieved through the combination of both an ideal three-dimensional (3D) structure (*x*, *y*, *z*) and suitable kinetics (*t*). Although the molecular architecture of metal complexes can be precisely analyzed by X-ray crystallography and other spectroscopic methods, their functions are not immediately apparent from their structures. We must combine many reaction parameters, such as temperature, pressure, solvent, additives to achieve truly efficient AH.[27] Certain asymmetric catalyzes such as the chiral amino alcohol mediated reaction of dialkylzinc compounds and aldehydes are known to show an enormous nonlinear relation between the enantiomeric purity of the chiral catalyst and product, because coexisting catalyst enantiomers interact with themselves or with other chiral or achiral molecules.[28] Thus, asymmetric catalysis is a pervasive endeavor lying outside the realm of traditional organic synthesis. The 4D chemistry is particularly important for industrial applications, which tend to involve many elements of chemistry and chemical engineering.[6]

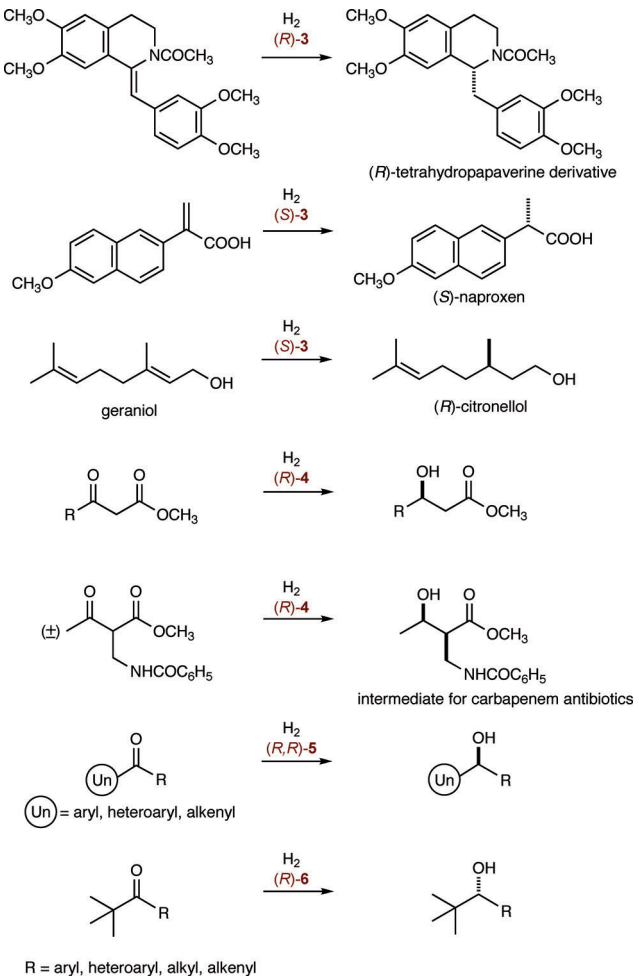
The BINAP/Rh catalyst **2** offered no advantage over other candidates. Thus, our high hope turned to disappointment. In fact, the asymmetric Rh chemistry in Scheme 3 (M = Rh), which had a splendid appearance with near-perfect *S*-selectivity, was evaluated as the worst from a logical point of view. As pointed out by Halpern, Brown, and their respective co-workers,[29,30] the AH reaction starts from the C=C/NHC=O chelate complex formed reversibly from the enamide substrate and (*R*)-**2** (L = alcohol), and hence the overall *S*/*R* selectivity is determined by the equilibrium ratio of two diastereomeric Rh complexes and their relative hydrogenation activity. Notably, AH is a purely kinetic phenomenon based on the Curtin–Hammett principle. Here the relative stability of the substrate/Rh complexes is in serious contradiction with the reactivity. The ^{31}P NMR spectrum of a 1:6 mixture of (*R*)-**2** (L = CH_3OH) and the enamide ($R^1 = H$, $R^2 = C_6H_5$) in methanol displayed a single set of eight-line signals. The enamide enantioface differentiation was excellent, as we correctly expected from the 3D shape of BINAP (Figure 2).[24a] Yet this thermodynamically favored enamide complex is not very reactive for hydrogenation. Instead, the NMR-undetectable, less stable Rh complex is much more reactive, and leads to the observed (*S*)-amino acid product (Scheme 3). The stable major complex must be converted to the less stable diastereomer by decoordination/recoordination prior to its hydrogenation. Thus, this complicated mechanistic black box has only a very narrow window open for the highly enantioselective AH. I greatly appreciate the efforts of my young colleagues in finding it. The reaction must be carefully conducted with a very low substrate concentration and under a low H_2 pressure. Otherwise, both diastereomeric substrate/Rh complexes are competitively hydrogenated, resulting in a moderate enantioselectivity. Such an aspect of AH is distinct from formally similar enzymatic catalysis where the enzyme/substrate binding specificity is imperative. Thus the substrate scope of this AH was very narrow. In addition to the difficulty in accessing enantiomeric BINAP,[24] this was a main reason for the retardation in publication. Indeed, I recall that the study of BINAP/Rh-catalyzed AH in the 1970s was a nightmare for our research group.

4. Ruthenium, an Element of Trust

The mechanistic problem was overcome when we replaced the Rh^I center by Ru^{II}.[14,31,32] These two metallic elements behave in a completely different fashion in the AH cycle. Rh first interacts with an enamide substrate and then reacts with H_2 (unsaturate/dihydride mechanism), while Ru cleaves H_2 to form RuH prior to interaction with an enamide (monohydride/unsaturate mechanism).[32] This mechanistic distinction results in the opposite asymmetric bias in AH of dehydroamino acids, as illustrated in Scheme 3. The (*R*)-BINAP/Rh catalyst ((*R*)-**2** (L = CH_3OH)) affords the *S* hydrogenation product as described above,[23] while the (*R*)-BINAP/Ru catalyst ((*R*)-**3** (Ar = C_6H_5, R = CH_3)) affords the

R product ($R^1 = R^2 = CH_3$) while maintaining an equally high degree of enantioselection.[31,32]

The utility of Ru^{II} is enormous, and provided a breakthrough in AH chemistry. Since 1986, we have invented a range of BINAP/Ru catalysts, as shown in Scheme 2, which allow for production of a wide range of enantiomeric organic compounds.[14] A variety of olefins can be used as AH substrates under mild conditions, as exemplified in Scheme 4. This story has already been reviewed elsewhere.[14,34]



Scheme 4. Asymmetric hydrogenation of olefinic and ketonic substrates.

The simple anionic ligands on Ru are not innocent. The BINAP/Ru diacetate **3** ($Ar = C_6H_5$, $R = CH_3$), though excellent for the AH of functionalized olefins, was totally inactive for structurally similar ketones such as β-keto esters. This result was unexpected. The use of halide ligands was a simple solution to this problem, because the hydrogenation mechanism needs an acid.[14,35] In the induction step of AH, BINAP/RuX_2 **4** reacts with H_2 to generate a necessary strong acid HX (X = halogen) together with a RuH catalyst, whereas the diacetate **3** ($R = CH_3$) merely forms the weaker acetic acid.[27] Subsequently, this AH with **4** was extended to a diverse array of functionalized ketones with consistently high enantioselectivity, as exemplified in Scheme 4.[14,34]

One might expect that the hydrogenation of simple ketones would be easier than the reaction of structurally elaborate ketones. This is not true. The BINAP/Ru catalyst (*R*)-**4** ($Ar = C_6H_5$, X = Cl) smoothly hydrogenates methyl 3-oxobutyrate in aqueous acetone, giving methyl (*R*)-3-hydroxybutyrate in 99% *ee* without hydrogenating the solvent acetone, which is structurally the simplest ketone and present in a large quantity. AH of the β-keto ester proceeds via a structurally well-organized chelate intermediate or transition state. Therefore, the presence of the ester group, a heteroatom functionality, interacting with the Ru center, is crucial for both the reactivity and stereoselectivity. Thus the simplest is not always the easiest.

Clearly, the AH of unfunctionalized, simple ketones was a long-standing synthetic problem. Fortunately, the invention of Ru complexes **5** (Scheme 2) possessing BINAP and a chiral 1,2-diamine ligand solved this fundamental problem (Scheme 4).[36] Now hydrogenation of simple ketones proceeds under neutral-to-basic conditions, in stark contrast to the reaction of β-keto esters occurring in the presence of a strong acid. This AH method is rapid, productive, and enantioselective. Notably, the diphosphine/diamine Ru catalyst is selective for a C=O linkage, whereas conventional phosphine/Ru complexes lacking an NH_2 ligand preferentially hydrogenate C=C bonds. Thus large-scale hydrogenation of unsaturated ketones no longer requires metal hydride reagents such as $NaBH_4$. The mechanistic scrutiny revealed that the reaction occurs by a nonclassical metal-ligand bifunctional mechanism involving a coordinatively saturated 18-electron [(diphosphine)(diamine)RuH_2] species that utilizes the outer metal coordination sphere.[37] Neither ketone substrates nor alcohol products have interaction with the Ru center throughout the reaction. The Ru catalyst **5** activates only H_2, and not an unsaturated substrate. This mechanistic principle is different from that standardized in Figure 1. Furthermore, the BINAP/PICA Ru complex **6** (Scheme 2) allows for AH of various sterically congested *tert*-butyl ketones (Scheme 4).[38]

This chemistry utilizing the NH effect, initially developed in the ERATO Noyori Molecular Catalyst Project (1992–1997) of the Research and Development Corporation of Japan (now a part of the Japan Science and Technology Agency (JST)), was further extended to asymmetric transfer hydrogenation (ATH) of simple ketones and imines using organic hydrogen donors such as 2-propanol or formic acid.[39] The chiral η^6-arene Ru complexes **7** (Scheme 2) are among the most effective. We found the existence of a mechanistic network between AH and ATH, where the selection of the reaction pathway, AH or ATH, is highly dependent on reaction parameters such as acidity or basicity of medium.[40]

We learned from this very long lesson that designing an asymmetric catalyst requires an integrated molecular approach. All of our Ru-catalyzed AHs, exemplified in Scheme 4, commonly involve an octahedral BINAP/RuH species, but their reactivity is remarkably affected by other anionic or neutral ligands present in the remaining three coordination sites, depending on the olefinic and ketonic substrates.[27] The desired molecular function emerges by combining various steric and electronic properties and

reaction environments. Furthermore, both electronic attraction and steric repulsion kinetically cooperate in obtaining a high level of enantioselectivity and a satisfactory reactivity.[41]

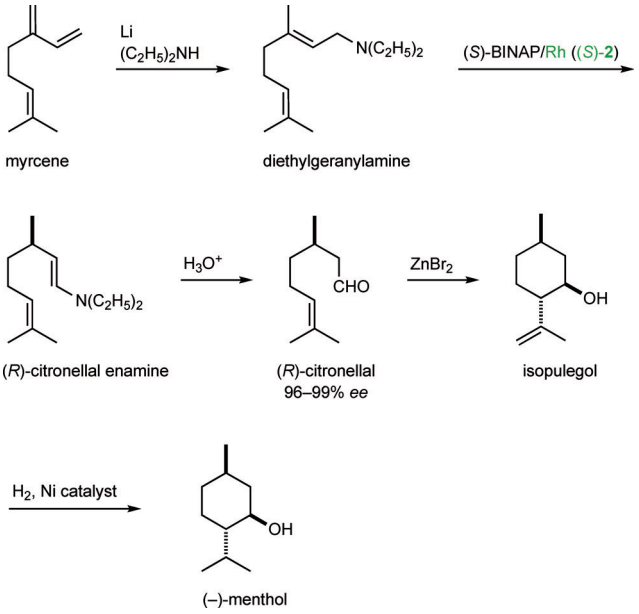
This practical AH method is useful for industrial synthesis of pharmaceutically significant chiral compounds. For example, carbapenem antibiotics are now best synthesized by using the AH of a racemic α-amidomethyl β-keto ester with (*R*)-**4** (X = Cl) under dynamic kinetic resolution, as shown in Scheme 4.[42] In a like manner, the simple AH of acetol to (*R*)-propanediol is used for the synthesis of levofloxacin (Cravit), a very important antibacterial agent developed by the Daiichi Pharmaceutical Company (now Daiichi Sankyo) in Japan.[43] Levofloxacin has been a virtual blockbuster, with annual sales of about 3 billion US dollars.

None of the other chiral catalytic systems offered this kind of generality. One can perform the Ru-catalyzed hydrogenation on a very large scale. The Takasago International Corporation established numerous AH procedures using the BINAP/Ru and other architecturally manipulated catalysts for the synthesis of biologically important chiral compounds. This AH technology has been applied worldwide in contract manufacturing, sales of catalysts and ligands, contract research, and patent licensing. The patent rights owned by JST, a public agency, were transferred to such companies as Takasago, Chirotech Technology in the UK, Dow Pharma in the US, and Dr. Reddy's Laboratories in India, among others. Obviously the endeavor of our research laboratories at Nagoya was limited, although many talented young colleagues and students contributed to this project. I do appreciate how the cooperation with industry helped to maximize the utility of our original scientific findings in AH.

It should be added that the Novartis Company in Switzerland commercially produces a famous herbicide, Metolachlor, by the Ir-catalyzed AH of an imine substrate.[6c] Looking back on the past four decades, I have seen AH grow from a single, bright point of light to a long, thick line in this century, and anticipate the continued extension of this remarkable science/technology as the thick line becomes a plane or even a three-dimensional space.[44] The possibilities for this core chemistry/technology are truly unlimited.

5. The Witch Is Capricious: The Utility of BINAP/Rh Complexes

The chiral BINAP/Rh complexes became famous immediately after their appearance in 1980, not as AH catalysts but for other purposes. Although our Rh chemistry was not beneficial for the initial purpose,[23] the cationic (*S*)-BINAP/Rh complexes, (*S*)-**2**, serve as excellent catalysts for the asymmetric 1,3-hydrogen shift reaction of allylic amines to give chiral enamines, which is a key step in the synthesis of (−)-menthol (Scheme 5).[45,46] This process was realized through fruitful academic/industrial collaboration. First, a research group at Shizuoka University found a regioselective method for synthesizing geranyldiethylamine by the LiN(C_2H_5)$_2$-catalyzed addition of diethylamine to myrcene.[47] Kazuhide Tani at the Otsuka Laboratory of Osaka University,



Scheme 5. Asymmetric synthesis of (−)-menthol.

who was a classmate of mine at Kyoto, happened to be struggling to find a catalyst for the asymmetric hydrogen-shift reaction of this allylic amine. The reactivity of Ti and Co catalyst systems was not satisfactory. He found a high reactivity of cationic Rh^I complexes but without suitable chiral ligands. Fortunately, the use of our newly developed BINAP/Rh complex, (*S*)-**2** (L–L = 1,5-cyclooctadiene, L = THF or acetone), instantly solved this problem.[48] Among the various candidates, only the BINAP ligand worked well, displaying an outstanding reactivity and enantioselectivity.

In 1983, technical refinements at the Takasago Company enabled industrial terpene production from myrcene (Figure 3).[49] This catalytic method allows a reaction using a 9-ton quantity of the geranylamine and 9.8 kg of the BINAP/Rh catalyst with 2.7 m^3 of THF per batch, giving a turnover number of 6800. The crystalline [Rh{(*S*)-TolBINAP}$_2$]ClO_4 catalyst can be recovered, with a very slight loss, and recycled. Currently, the Takasago Company is producing 2800 metric tons of (−)-menthol per year, which corresponds to about one-third of the world demand.[49c] This compact chemical process allows a more stable supply of this necessity, compared to the climate-variable natural production from peppermint, which requires a large land area. The 98% enantiomeric purity of synthetic (*R*)-citronellal is significantly higher than the 80% purity of the natural product collected from rose oil. Thus this process provides a convenient route to chiral citronellol as well.

The Takasago Company manufactures more than 3500 tons of optically active compounds per annum, and produces more than 350 tons for pharmaceutical use. We are grateful to the Takasago management for believing in our catalytic science and for taking the necessary business risks. This medium-sized company perceived the emerging technological potential differently from the larger Ajinomoto Company that first filed a patent for the BINAP/Rh catalyst.[25]

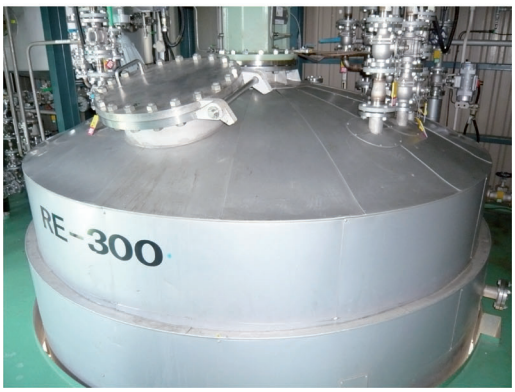


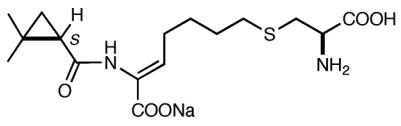
Figure 3. Menthol production at the Takasago Iwata Factory, Shizuoka. Top: The distillation towers for purification of geranyldiethylamine visited by R. Noyori (lower left-hand corner) in 1984. Bottom: The current (2012) reactor for the asymmetric 1,3-hydrogen shift reaction. Courtesy of the Takasago International Corporation.

Now, what is the major impact of our science on society, aside from the obvious economic benefits? In the early 1990s, 88% of synthetic chiral drugs were still racemic mixtures of both enantiomers, thereby reflecting the difficulty of practical asymmetric synthesis.[50] This situation was obviously irrational from a scientific point of view. Any problems arising from inappropriate chirality recognition in the human body should be avoided at all costs.[3] Thus, in 1992, the US Food and Drug Administration (FDA) set out guidelines for "racemic switches."[51] The new regulations strongly urged pharmaceutical companies to manufacture and commercialize purely single-handed compounds. However, in the 1980s, no such large-scale asymmetric synthesis existed anywhere else. I believe that this successful technology developed in Japan was a contributing factor to this important science-based decision, which resulted in major improvement in medicine. Later, thanks to the progress in asymmetric synthesis based on the endeavors of many researchers, the proportion of single-enantiomer drugs increased dramatically, and the worldwide sales of such drugs reached 123 billion US dollars in 2000,[52] and even 225 billion US dollars in 2005, representing 37% of the total pharmaceutical market of 602 billion US dollars.[53] The distribution of new pharmaceuticals approved by the US FDA in 2008 was as follows: 63% single enantiomers, 32% achiral compounds, and only 5% racemates.

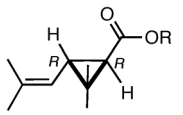
6. The Half-Century Voyage Traveled by a Small Seed

What is the destiny of our primitive finding shown in Scheme 1?[4] Forty-six years ago in Kyoto, we were excited about the discovery of the first asymmetric cyclopropanation, though at the time it was practically meaningless. Although I wondered what this original finding might lead to in the many years ahead, honestly, I could not think of any practical application. Then I left this line of chemistry and never returned. However, the scientific essence of this discovery did not disappear, and in fact the reaction was steadily improved in efficiency through the development of new chiral catalysts by many other groups.

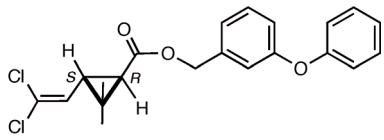
A student who happened to be in the Nozaki laboratory when we developed the asymmetric reaction was Tadatoshi Aratani. After obtaining his doctorate, Aratani went to work for the Sumitomo Chemical Company, where he developed an excellent chiral Cu catalyst and established an industrial synthesis of (*S*)-2,2-dimethylcyclopropanecarboxylic acid, a building block of cilastatin, which was developed by the Merck Company in the US (Figure 4).[54] Cilastatin serves as



cilastatin



chrysanthemates



permethrin

Figure 4. Sumitomo asymmetric synthesis of cyclopropanes and the Olyset Net project in Tanzania. Courtesy of the Sumitomo Chemical Company.

an in vivo stabilizer of the antibiotic β-lactam imipenem. This commercial success occurred in the 1980s. Around the same time, Sumitomo also succeeded in the large-scale synthesis of chrysanthemic esters, which are potent insecticides. But, although the technology had been realized, it was never commercialized because there was an unexpected decline in the mosquito population in Japan.

More recently, however, there has been a totally unforeseen development in fighting malaria because of the need to minimize the use of DDT, which causes the spread of drug-resistant strains and ecological turbulence through food chains. Thus the technology developed by Sumitomo Chemical[55] is now being used in Tanzania in response to the World Health Organization's "Roll Back Malaria" campaign initiated in 1998.[56] Every year, 300 to 500 million people are infected with malaria by the Anopheles mosquito. Of this number, more than 1 million, most of them children, die of the disease, one every 30 seconds. Around 90% of these deaths take place on the African continent, south of the Sahara Desert, and the economic loss is estimated at around 10 billion US dollars. Sumitomo Chemical incorporated permethrin into high-density polyethylene fiber to manufacture Olyset Nets (Figure 4), which allow the very gradual release of the pyrethroid over five years. Since 2003, this long-lasting insecticidal net technology has been provided to Tanzania free of charge. Consequently, some 8000 new jobs were created, and the school facilities were significantly improved. This beneficial activity is further being extended worldwide.

Roughly half a century has passed since we made a small discovery in Kyoto. Who would have thought that the small chemical seed planted so many years ago would eventually make such an important contribution to global welfare? I wonder what lessons we will take from this story. What does it teach us about science, technology, and societally beneficial innovation? And what are the necessary factors to bring this all about? The scientific community, and members of industry, government, and many other sectors must carefully rethink these issues.

7. Where Did I Come From?

"Science has no borders, but scientists have their fatherlands" said Pasteur. Researchers are human beings and their environment is socially founded. Therefore, my path of life is in many ways much different from that of Americans, Europeans, or even other Asians. My career as a scientist has been full of challenges, excitement, and joy, but at the same time, I have also had to overcome many obstacles. My own experience makes me think: what is behind the talent and intuition of a Japanese scientist?

In 1938, I was born in Kobe, a city in Japan, as the first son of Kaneki and Suzuko Noyori. At the very end of World War II, in 1945, just when I was to enter elementary school, US Air Force B29s heavily bombed Kobe, reducing the central city to ashes. Our family took refuge for a while in the nearby countryside. Even after the war ended, my childhood was still difficult and our country was terribly short of food and supplies. Thus our family of six lived frugally.

I wanted to become a scientist ever since I was a small child under the influence of my father, a gifted research director of a chemical company. In 1949 when I was 11 years old, Professor Hideki Yukawa was awarded the Nobel Prize in Physics. He was the first Japanese to receive a Nobel Prize. I was especially delighted with this great event, because he was an acquaintance of my parents. Shortly after this event, in 1951 when I had just entered junior high school, my father took me to a conference on a new fiber called nylon. I was the only child in the audience. The lecturer, the President of the Toray Company, which had acquired the technological license from the DuPont company in the US, proudly explained, "this new fiber can be synthesized from coal, air, and water and it is thinner than a spider's thread, yet stronger than a steel wire." I was highly impressed. Here was a new material created by chemistry from almost nothing. This was when I began to dream of becoming a chemist who would invent all kinds of materials beneficial to society and Japan's economic recovery from the devastation of war.

In middle school in Kobe, my favorite subjects were mathematics and science. My first chemistry lesson was given by Kazuo Nakamoto, who had been dispatched from Osaka University and afterward became an inorganic chemistry professor at the Illinois Institute of Technology and later Marquette University in the US. My appetite for chemistry was further whetted by the guidance of many enthusiastic teachers. Another person I admired in this connection was Professor Ichiro Sakurada at Kyoto University, who invented vinylon, the first Japanese-made synthetic fiber. He was one of the reasons I decided to study chemistry at Kyoto. Professor Yukawa was also at Kyoto University but in the physics department. At the time, the chemistry departments in the faculty of engineering were attracting the best high school students in connection with the rapid development of the petrochemical industry.

I entered Kyoto University in 1957, the year the Soviet Union launched its artificial satellite Sputnik into space, which clearly demonstrated the power of science-based technology and also shocked young science students in Japan. After three years, I began to study organic chemistry under the guidance of Professors Keiiti Sisido and Hitosi Nozaki. Japan's economy had been improving but was still not robust enough to promote high-level education/research in science. In the laboratories, the structures of organic compounds were determined largely by combustion analysis. The hand-operated Beckman UV/Vis spectrometer was the sole reliable spectroscopic tool. The whole of Kyoto University was equipped with only one IR spectrometer. There was no NMR instrument installed at this leading university, and only a national nuclear energy research institution and one private company owned primitive 40 MHz machines. Because of the absence of analytical instruments, imaginative students were free to enjoy various speculations. Since neither silica gel nor active alumina was available for chromatography, recrystallization or derivatization to crystalline compounds was crucial for obtaining analytically pure substances. Oily compounds were purified by large-scale distillation or sometimes steam

distillation. Students had to be highly skilled. Because only very limited kinds of solvents and reagents were commercially available, we had to synthesize the necessary materials according to the standard procedures in *Organic Syntheses*. For example, we synthesized benzophenone, triphenylphosphine, diborane, and even the solvent dimethoxyethane. Reactions were conducted on a rather large scale using a 0.5–2 L vessel. We worked very hard in the department library. *Chemical Abstracts* was indispensable, because access to original literature was limited. Reading the literature, I recall, was more serious than it is now, because photocopying machines did not exist at the time, even in the US and Europe. We had to make an abstract or take full notes. A skillful typist was needed to make a manuscript for publication, and carbon copies were used for duplication. Mimeographing was necessary for distributing copied materials at meetings. As such, everything was inefficient and the progress of research was very slow. However, students were highly motivated, and the situation was much improved by the mid-1960s.

At the time, Japan had a long-held tradition in natural products chemistry, which was further strengthened by the 1964 IUPAC conference held in Kyoto. In addition, industry-oriented synthetic polymer chemistry had been flourishing in the Faculty of Engineering because of its connection with economic activity. However, the standard of organic chemistry was still not very high, except in a few special cases such as Japan's traditional nonbenzenoid aromatic chemistry. Our way of thinking remained empirical, but we young researchers and students were encouraged to think more logically by Charles C. Price of the University of Pennsylvania, who stayed in Kyoto in 1963 to give an intensive lecture course on physical organic chemistry.

Completing my master's degree in 1963, I was appointed as instructor in the Nozaki group at Kyoto University, even though I did not yet have my doctorate. This was possible in the Japanese university system, and I eventually obtained the degree of Doctor of Engineering in 1967 by submitting a thesis to the department. I initially intended to work in industry because of the family circumstances in which I was brought up, but this appointment irreversibly destined me to pursue science in academia. Then, as a subgroup leader of the Nozaki lab, I started to study short-lived organic intermediates and photochemistry and, as a consequence, encountered the above-mentioned asymmetric cyclopropanation.[4]

Creativity often emerges at the interface of different disciplines. In the mid-1960s, many researchers who focused on organic structures and reaction mechanisms were totally indifferent to inorganic coordination chemistry. However, I was highly impressed by a brief account given by Jack Halpern in *Chem. Eng. News* in 1966,[57] in which he stated that d^8 Rh^I complexes behave similarly to structurally simple six-electron carbene species. That is, Rh^I species, like singlet CH_2, react with a C=C linkage to form a π complex or metallacyclopropane and also insert into an H–H, H–X, or C–X bond. Similarly, d^6 Ru^{II} and d^7 Co^{II} complexes act like six-electron carbocations and seven-electron free radicals, respectively.[57,58] This simple analogy convinced me of the bright future of organometallic reagents and catalysts. This was when I departed from classical organic chemistry and shifted to organometallic chemistry for organic synthesis (OMCOS).

In the fall of 1967, when I had just been awarded my doctorate degree, I received a surprising invitation from Nagoya University to chair a newly founded research group as an associate professor. This chemistry department was famous for research on natural products chemistry led by the renowned Professor Yoshimasa Hirata, who fostered the development of Koji Nakanishi (Columbia University), Toshio Goto (Nagoya University), Osamu Shimomura (Marine Biological Laboratory, Woods Hole; a 2008 Nobel Laureate), Yoshito Kishi (Harvard University), and many others. I accepted this honorable offer and launched my own research group the next spring when I was 29 years old.

I decided to focus my research on OMCOS to create a new stream at Nagoya, but at the time I strongly hoped to broaden my scientific expertise by studying abroad. Thus in 1969, when the US space development project first succeeded in sending men to the moon in Apollo 11, I joined the Corey group at Harvard University as a postdoctoral fellow. I immediately noticed that the Harvard chemistry department was a colorful collection of 20th century heroes of organic chemistry, including Robert B. Woodward, Louis F. Fieser, Paul D. Bartlett, Frank H. Westheimer, and William von E. Doering, in addition to my supervisor E. J. Corey. The regular department seminars were highlighted by the active participation of these academic giants. Also I was astonished by the substantial gap in the research conditions and also living standards between the US and my home country. At Harvard, we could purchase a variety of reagents, catalysts, and purified solvents as well as high-quality TLC plates and many other disposables unavailable in Nagoya. Dry ice and liquid nitrogen as coolants were available anytime free-of-charge for our experiments. We postdoctoral fellows were paid some 600 US dollars per month, while the monthly salary of an associate professor at Nagoya, chairing an independent research group, was a mere 65 US dollars (back then 1 US dollar = 360 JP yen, not 80 JP yen as now). Most importantly, my major asset from my stay was the warm friendship of many promising students and postdoctoral fellows of the chemistry department who, at the time and later, helped and guided me in many ways. For example, K. Barry Sharpless, a fellow 2001 Nobel Laureate, was then a postdoctoral fellow in Konrad Bloch's biochemistry research group and helped me in my task on selective hydrogenation of a $PGF_{2\alpha}$ derivative. Since HPLC was yet undeveloped, his special TLC technique using an $AgNO_3$/acetonitrile-impregnated silica gel plate was extremely effective for analyzing the structurally very similar olefinic compounds. His advice played a key role in solving my research problem.[17] Richard R. Schrock, a 2005 Nobel Laureate, was a graduate student working under John Osborn and assisted me in my hydrogenation work by supplying a precious sample of a new Rh complex. Today, the alumni of the Corey school are spread across the world, in both academia and industry, making a tremendous contribution to the establishment of modern organic synthesis.

In 1972, shortly after returning to Nagoya, I was promoted to professor and then married Hiroko Oshima. Later we had two sons, Eiji (staff writer for a newspaper company) and Koji

(modern art painter). I dedicated more than three decades at Nagoya in education, research, and administration before moving to RIKEN as President in 2003. I was heavily involved in organic synthesis, molecular catalysis, and more recently "green chemistry", which is a requisite of modern chemical synthesis.[59] Hisashi Yamamoto, a student of Nozaki and then Corey, had long walked with us on the same OMCOS avenue in Nagoya.

Life was difficult for my generation as we struggled to overcome economic difficulties not only in our childhood but even into our early university years. The standards of living in Japan had recovered to a reasonable level only by the early 1980s. It is obvious that our harsh situation induced us to think differently from researchers in the US and Europe. I do not want any of our next generation to have to undergo the same kind of difficulties, but it is true that the poverty of our youth helped to make those of my generation creative and emotionally strong. The Great East Japan Earthquake on March 11, 2011 left hundreds of thousands of victims in its wake. The most tragic are the 1600 children who lost at least one parent and the approximate number of 260 children among them who lost both parents. To be orphaned is a terrible fate, but I sincerely hope that at least some of these children will overcome their misfortune to become creative scientists. Likewise, I am hopeful of a similar growth of young cohorts in the currently developing Asian and African countries.

8. The Enchanting Molecular Beauty of BINAP

What is the origin of unique creativity in scientific research? I strongly believe that, in addition to the experiences of childhood and youth, including family environment and education, ethnic culture is important in nurturing scientists. Culture is a strategy of our species for survival. Science and art are undertakings common to all humanity, as seen in the prehistoric drawings of hunting scenes and dynamic renditions of deer and bison in the Altamira Cave in northern Spain. They are both an important elements of culture; in fact they are essential to our very existence. Put another way, science and art can be viewed as humanity's dialogue with nature.[60] Both the scientist and artist seek through their work to elevate and express themselves, and both enrich our lives spiritually and materially. Science and art originate from the same source, and the only difference is in emphasis.[61] As such, it is a puzzle to me why, as Charles Percy Snow wondered in his famous Rede Lecture "The Two Cultures", given in Cambridge in 1959,[62] there has not been more sharing between scientists and artists in the areas of intellect, sensibility, and technology. Science and art are said to be frequently at odds with each other, two cultures in conflict that never communicate. If this is true, I am afraid it represents a serious threat to research culture, because excellence in scientific research certainly requires intellect, aesthetic sensitivity, and superior technology.

The artist is not a scientist. Nevertheless artistic inspiration is strongly linked to cultural background and scientific and technological events, which are grounded in the same rational foundation. In 1907, Pablo Picasso painted his famous *Young Ladies of Avignon* (*Les Demoiselles D'Avignon*), replacing traditional perspective with cubism. According to Arthur Miller, the unmatched originality of this "simultaneous vision" was inspired by a series of modern technologies invented at the end of the 19th century.[63] The advent of the telephone, radio, automobile, airplane, and other inventions convinced Picasso, a Spanish artist who was living in Paris at the time, that a whole subject could be portrayed as an entirety only by moving himself to view it from all possible angles. The discovery of X-rays, radioactivity, and electrons is also thought to have played their part in emboldening him to tackle this new concept. In art, as in science, "seeing may be believing", but the truth is not always visible to the naked eye.

Thus a scientific endeavor is also a work of art. Science is objective, but scientific research is a human activity. I have traveled to more than 40 countries or regions and have enjoyed the cultural differences. There are ethnic and regional characteristics in approaches to research.[64] Although modern science in Japan has a mere 150-year history, our nation has long been nurtured by a unique cultural tradition of nature appreciation that goes back more than 1500 years.

Asymmetric catalysis is an art and design focusing on a dynamic molecular function. The scientific subject must not only be technologically efficient but also satisfy the intellect and sensibility of researchers. Scientific endeavor is totally borderless and inevitably dependent on international cooperation. Still, I feel my life as a scientist has been guided, at least partly, by the beauty of Japanese arts and crafts.

Science is descriptive out of necessity. However, I have long felt it difficult to properly represent its innermost essence, particularly in a foreign tongue. Regretfully, I have evaded pioneering stronger and more lucid forms of expression. The expression of scientific essence, I feel, is found in both its abstractions and in its concrete representations. The abstractions give science its universal character while its concrete representations have a powerful immediate impact.

Back to our research: since the central metal in the organometallic asymmetric catalyst (Figure 1) is intrinsically achiral, a suitable molecular design of chiral ligands (or a chiral arrangement of ligands) is essential. In the mid-1970s at Nagoya, I decided to explore the general use of an atropisomeric C_2-chiral binaphthyl scaffold for asymmetric synthesis and catalysis, because this artificial molecular architecture is quite simple and distinctly beautiful. I recall that, at the time, synthetic chemists used largely natural product-derived auxiliaries or ligands that possessed a rigid structure with a nonsymmetrical, central chirality.

Any purposive molecular design must be rational. In this regard, the C_2 symmetry of bifunctional binaphthyls simplifies the chemistry by halving the number of possible diastereomeric species present during reaction. In our research program along this line, we first invented a binaphthol-modified lithium aluminum hydride reagent, BINAL-H, for asymmetric reduction of ketones, which solved the "15*S* problem" in Corey's commercial synthesis of prostaglandins.[65,66]

The long-sought BINAP is a fully aromatic diphosphine simply composed of four benzene rings, two naphthalene

units, and two phosphorous atoms. Both benzene and naphthalene are fundamental organic compounds that are highly symmetrical, rigid, and static in nature. On the other hand, the resulting BINAP is axially dissymmetric, pliant and dynamic, and also functional. Being fully composed of sp^2 carbon atoms, this molecule is architecturally well ordered yet flexible. As is seen in Figure 2, the fully aromatic diphosphine ligand accommodates various transition metals M by rotating about the binaphthyl C(1)–C(1′) pivot and the C(2 or 2′)–P bonds without any serious increase in torsional strain, yet maintaining its skeletal unambiguity. An X-ray crystallographic study of the BINAP/Rh complex, (*R*)-**2** (L–L = norbornadiene), indicates that the induced-fit coordination of (*R*)-BINAP to the Rh atom forms a λ-skewed seven-membered chelate ring with a dihedral angle of the two naphthalene planes of 74.4°and a P-Rh-P bite angle of 91.8°.[26,67] Instead, the Ru analogue, (*S*)-**3** (Ar = C_6H_5, R = $C(CH_3)_3$), possesses a much smaller dihedral angle of the two naphthalenes, 65.6°, while keeping a similar P-Ru-P angle of 90.6°.[31a] Furthermore, the BINAP/metal element in Figure 2 (M = Rh or Ru) can accommodate various atoms and functionalities on the green-colored coordination sites through a suitable BINAP conformational change, which includes the P–phenyl bond rotation. Overall, the chiral reactive metal intermediates clearly define the asymmetric sense of interligand reaction in the molecular cavity, or sometimes the reaction occurring on its surface. Notably, the skeletal pliancy or flexibility in solution, offering the transition-state stabilization, differs from structural flaccidness, which generally leads to inferior stereoselection.

The architectural characteristics of BINAP fit well with the sensibility of Japanese scientists (and perhaps scientists of some other ethnicities). The molecular beauty satisfies our sense of grace. Many family crests of Japanese clans possess a pattern with a plane symmetry or rotation symmetry, as exemplified in Figure 5.[68] One is a plane-symmetrical rigid crest made of four squares. The other has a rotation symmetry formed from two alternately arranged oriental fans and has a soft image. Japanese are said to prefer rotation symmetry, while Westerners prefer plane symmetry.[69] It has also been noted that we prefer soft structures while Westerners prefer rigid structures. For example, Japanese take special pleasure in the pliancy of bamboo, finding bamboo groves and objects made of bamboo equally beautiful and comfortable.

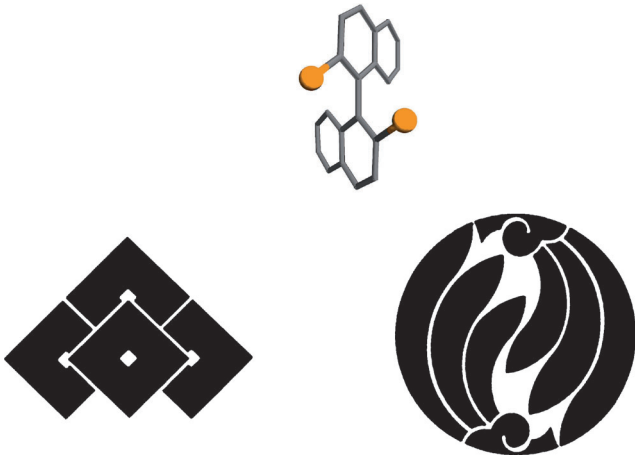


Figure 5. Plane symmetry and rotation symmetry.

The asymmetric catalysts in Scheme 2 are a kind of high-quality craftwork. Molecular arts is useful in the real world. Soetsu Yanagi (1889–1961), a founder of the Japanese folk craft movement, often spoke of "Yo-no-bi", a Japanese term referring to the beauty of function.[70] As he maintained, "Beauty in crafts is identified with use. It is beauty born of use. Apart from use there is no beauty of craft." Likewise, the Bauhaus movement, started in 1919 in Germany (but closed in 1933 under pressure from the Nazis) by the architect Walter Adolph Georg Gropius, who sought to fuse industrial technology with art, also spoke of "functional beauty".[71] I totally agree with these activities and cultural philosophy. Overall, the sources of scientific serendipity are highly complex.

9. Epilogue

The passage of our life is decided by innumerable coincidences and a very few inevitabilities. Here, I have been given an opportunity to reflect on my half-century of experience as a chemist. Fortunately, some of the dreams of the Don Quixote at Nagoya did come true in partnership with quite a few Sancho Panzas, as partly quoted in references in this Essay.

I believe that basic science is the fountainhead of human knowledge and as such has eternal cultural value. The technology that we gain from our scientific knowledge is the foundation of civilized society. And creative innovation derived from science and technology is what makes us internationally competitive and assures our continued survival as independent nations. Furthermore, innovation is also an essential aspect of our international cooperation to assure the continued survival of humanity.

I have found that it is not easy to plan a great discovery or invention. Scientific discovery requires intellect, sensibility, and superior skills and technology. But there is one more thing we need, and that is luck. To invent superior technology we must bring together and consolidate knowledge. At the same time, researchers and engineers must be convinced that they will succeed. And when it comes to innovation that has social or economic value, they need not just knowledge, but also wisdom, where interdisciplinary cooperation is often crucial. Other factors that will affect the results are part of the social fabric and include such things as the era, region, and culture in which individuals are working. The way things are right now and how they will be 50 years from now will certainly be very different, just as the social elements of our region will be very different from those in the European, American, Arabic, or African countries.

The principle of our science is no different from the law underlying the whole scientific realm. However, synthetic chemistry faces more than just intellectual challenges. Resolving a range of scientific and technological problems reveals that superficial novelty does not make any sense. Because of the ever-increasing significance of our endeavor,

we must pursue "practical elegance".[72] I have noticed that only truly useful methods or processes can survive in our world. I recall that any solution we achieved could never be universal but is only limited to a very specific problem. So every tiny satisfaction in my research was followed by even greater self-reproach. Although academic research has brought me spiritual exaltation, the resulting scientific publications may be no more than self-contentment of no practical significance. What social values may have been generated from our small seeds of endeavor was achieved largely through cooperation with colleagues in other institutions. I have been fortunate enough to interact with many active industrial researchers and, consequently, provided a proof of our scientific concept. Any recognition of my life-long academic achievements must include these colleagues as well.

Researchers in various positions around the world are working hard to achieve their goals and everyday are discovering an incredible number of facts. But I have come to believe that the discovery of values, whether it is scientific, technological, or societal, is even more important than the discovery of mere facts. Researchers are advised to carefully evaluate the implications of their experimental results, even if those results are unsuccessful or incompatible with the original purpose. Your findings could be much more valuable than they initially appear, as exemplified in this article. Young researchers have great potential within them. I very much hope that they will come to fully realize their capabilities in their future activities in either science or society at large.

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