ASYMMETRIC CATALYSIS: SCIENCE AND OPPORTUNITIES

Nobel Lecture, December 8, 2001

by

RYOJI NOYORI

Department of Chemistry, Graduate School of Science, and Research Center of Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan.

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 differently. The structural difference between enanatiomers 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, resulting 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, reflecting the difficulty in the practical synthesis of single enantiomeric compounds[4]. In 1992, the Food and Drug Administration in the US 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 US dollars[6]. Thus, gaining access to enantiomerically pure compounds in the development of pharmaceuticals, agrochemicals, 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, enantiomeri-

186

cally 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, 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[7]. A small amount of a well-designed chiral catalyst can combine A and B, producing 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 where the maximum chiral efficiency can be obtained only by a combination of suitable molecular designing 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
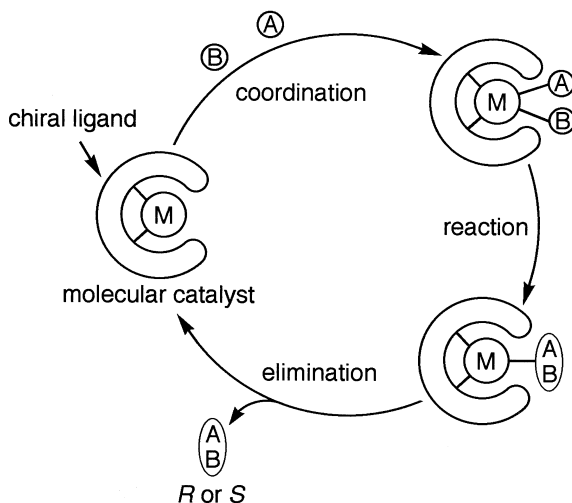

Figure 1. A general principle of asymmetric catalysis with chiral organometallic molecular catalysts. M = metal; A, B = reactant and substrate.

187

(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. 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.

DISCOVERY OF ASYMMETRIC CATALYSIS VIA CHIRAL ORGANOMETALLIC COMPLEXES

In 1966, when I was in H. Nozaki's laboratory at Kyoto, we discovered the first example of asymmetric catalysis using a structurally well-defined chiral transition metal complex[8]. This finding resulted from research done for an entirely different purpose which was to elucidate the mechanism of carbene reactions. As illustrated in Figure 2, when a small amount (1 mol%) of a chiral Schiff base–Cu(II) complex was used as a molecular catalyst in the reac-
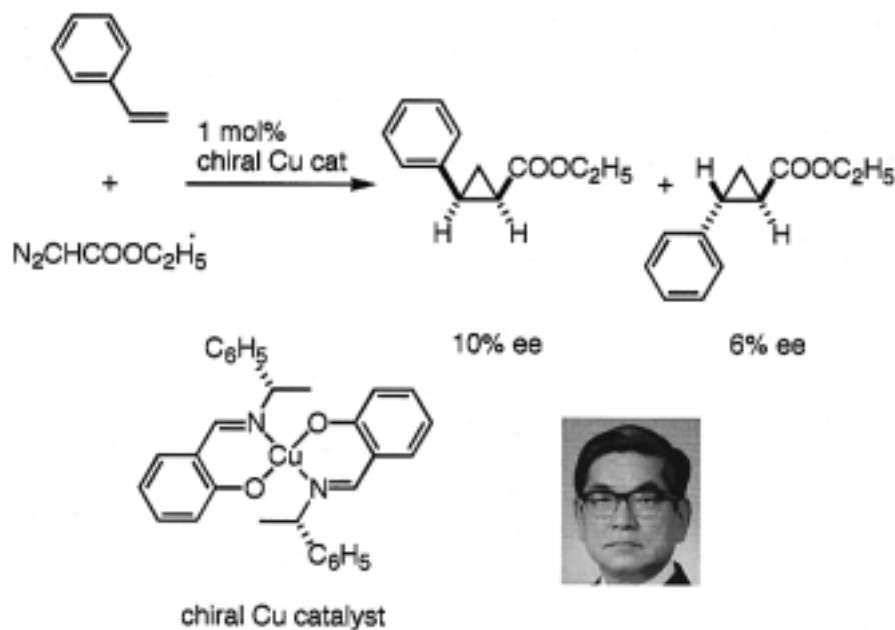

Figure 2. Discovery of asymmetric reaction by means of a chiral organometallic molecular catalyst. Photo: Professor H. Nozaki (1985).

tion 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 carbene insertion to a C–O bond of 2-phenyloxetane giving optically active 2,3-substituted tetrahydrofuran derivatives. At that time, the finding was synthetically primitive since the degree of enantioselection was meaningless practically. Later, T. Aratani, a Kyoto student, went to Sumitomo Chemical Co., where he invented an excellent chiral Cu catalyst for asymmetric cyclopropanation, achieving the industrial synthesis of chrysanthemates (efficient insecticides) and (*S*)-2,2-cyclopropanecarboxylic acid. The latter compound is a building block of cilastatin, an in vivo stabilizer of the carbapenem antibiotic, imipenem (Merck Co.) (Figure 3) [9].

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
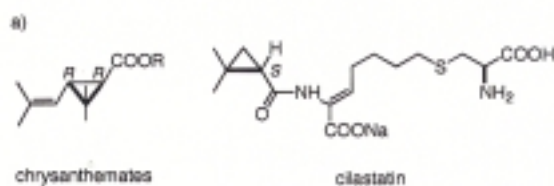
Figure 3. Sumitomo asymmetric cyclopropanation. a) Useful chiral cyclopropanes and b) reaction apparatus.

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 H_2 by a transition metal complex in the late 1930s (M. Calvin, 1961 Nobel laureate)[10]; homogeneous hydrogenation of olefinic substrates with $RuCl_3$ in 1961 (J. Halpern, J. Harrod, and B. R. James)[11]; and hydrogenation of olefinic compounds using $RhCl[P(C_6H_5)_3]_3$ in 1965 (G. Wilkinson, 1973 Nobel laureate)[12]. Most importantly, in 1956, S. Akabori at Osaka reported that metallic Pd drawn on silk catalyzes asymmetric (heterogeneous) hydrogenation of oximes and oxazolones[13]. 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)[14] and L. Horner[15] reported independently the first homogeneously catalyzed asymmetric hydrogenation of olefins with chiral monodentate tertiary phosphine–Rh complexes, albeit in 3–15% optical yield[16]. H. B. Kagan provided a major breakthrough in this area in 1971, when he devised DIOP, a C_2 chiral diphosphine 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[17]. The Knowles group at Monsanto established a method for the industrial synthesis of L-DOPA, a drug for treating Parkinson's disease, using his DIPAMP–Rh catalyzed asymmetric hydrogenation as a key step[18]. 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 = C bonds in a prostaglandin $F_{2\alpha}$ derivative to the $F_{1\alpha}$ form having only one C = C bond[19]. 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 $RhCl[P(C_6H_5)_3]_3$[12] 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 phosphine–Rh complexes could hydrogenate satisfactorily only dehydro amino acids but not many other olefins. Asymmetric hydrogenation of ketones was totally unexplored[20].

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, developing an excellent chiral ligand is crucial. Attracted by its molecular beauty[21], we initiated the synthesis of BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)[22] 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 diphosphine 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 diphosphine 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 (Figure 4a). However, this seemingly straightforward synthetic pathway was not reproducible due to the tendency of the chiral intermediates to cause racemization[23]. In 1978, we found a reliable method for resolving racemic BINAP with an optically active dimethyl(1-phenylethyl)amine–Pd(II) chloride complex[22], while later optically pure BINAP became available more conveniently by resolution of BINAP dioxide with camphorsulfonic acid or 2,3-O-dibenzoyltartaric acid (Figure 4b)[24,25]. Although the elusive BINAP was available, achieving our goal was
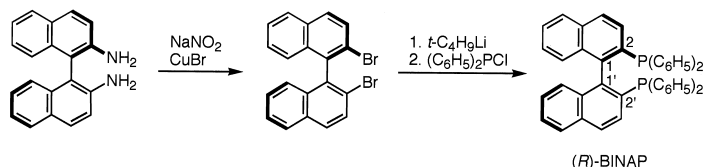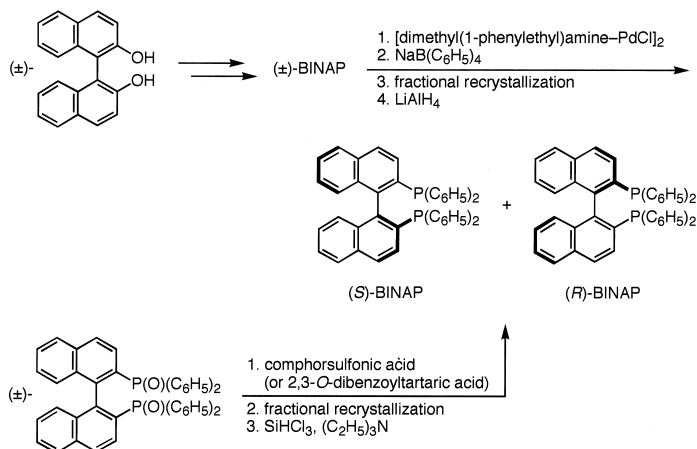

Figure 4. Access to enantiomerically pure BINAP.

191

still in the distance. Enantioselectivity of BINAP–Rh(I) catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids was highly variable and not satisfactory at that time, ee of the chiral products being at most about 80%. However, we remained patient. In 1980, six years after the start, thanks to the unswerving 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 diphosphine, 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^2 carbon atoms are in turn skeletally 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.

ASYMMETRIC SYNTHESIS OF MENTHOL

The cationic BINAP–Rh complex was best used in asymmetric isomerization of allylic amines[27], realizing an industrial synthesis of (–)-menthol from myrcene (Figure 5)[28]. This resulted from a fruitful academic/industrial
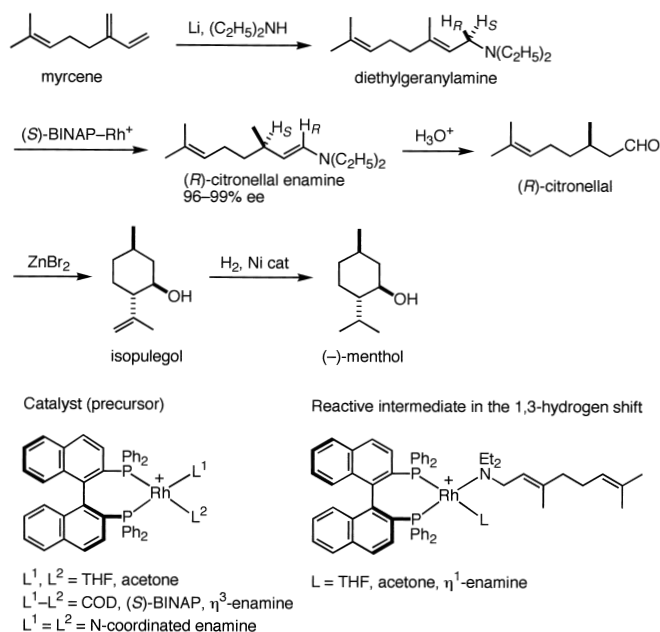

Figure 5. Takasago menthol synthesis.

collaboration between groups at Osaka University (S. Otsuka and H. Tani)[29], Nagoya University (R. Noyori), Institute for Molecular Science (H. Takaya), Sizuoka University (J. Tanaka and K. Takabe)[30], and Takasago International Co.(Figure 6). The key step was the asymmetric isomerization of geranyldiethylamine catalyzed by an (*S*)-BINAP–Rh complex in THF 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* hydrogens on the flexible allylic amine skeleton during the 1,3-suprafacial shift that occurs via a nitrogen-triggered mechanism[31]. The asymmetric reaction is performed on a nine-ton scale. The full technical refinements of the position- and stereoselective addition of diethylamine to myrcene, giving the starting geranylamine, and the $ZnBr_2$-catalyzed intramolecular ene reaction of (*R*)-citronellal, forming 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[28,29].

Figure 6. 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.

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[32] and also from the use of Ru element that behaves differently from conventional Rh[33,34]. The cationic BINAP–Rh complexes catalyze hydrogenation of α-(acylamino)acrylic acids or esters to give the corresponding amino acid derivatives of high ee (Figure 7)[22,23]. However, the reaction is relatively slow, and high enantioselectivity is obtained only under special conditions probably due to 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 diphosphine –Rh complex proceeds via 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, leading to the desired hydrogenation product, is present in a very small quantity and is even NMR-invisible in the equilibrium mixture[23a]. 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 8)[38,39]. The Ru complexes are excellent catalysts for asymmetric hydrogenation of various functionalized olefins, as summarized in Figure 9. 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[40] 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 α,β- and β,γ-unsaturated carboxylic acids takes place in alcoholic media, where the sense and de-
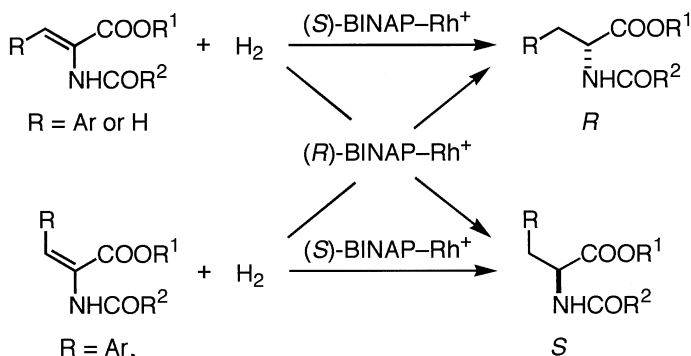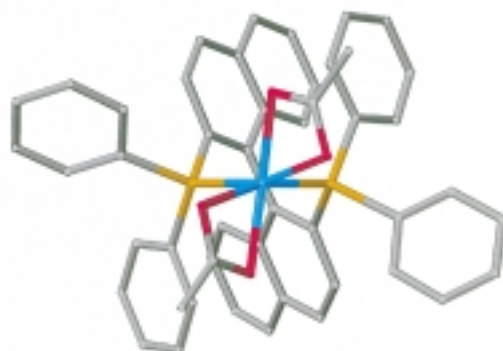

Figure 7. Asymmetric hydrogenation of α-(acylamino)acrylic acids catalyzed by BINAP–Rh complexes.

(R)-BINAP–Ru(II) diacetate

(S)-BINAP–Ru(II) diacetate

Figure 8. Structures of BINAP–Ru diacetate complexes.

gree of the enantioselection are highly dependent on the substitution pattern and hydrogen pressure[41]. Allylic and homoallylic alcohols are also hydrogenated with high enantioselection[42]. Certain racemic allylic alcohols can be resolved by the BINAP–Ru catalyzed hydrogenation[43]. The chiral Ru complexes effect highly enantioselective hydrogenation of (Z)-2-acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinolines[38,44]. In a similar manner, enantio-enriched α- and β-amino acids[45] as well as α-amino phosphonic acids[46] are obtainable from suitably amido-substituted olefins. Notably, the Ru(II) and Rh(I) complexes possessing the same BINAP chirality form antipodal amino acids as the predominant products[47].

Figure 10 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)-
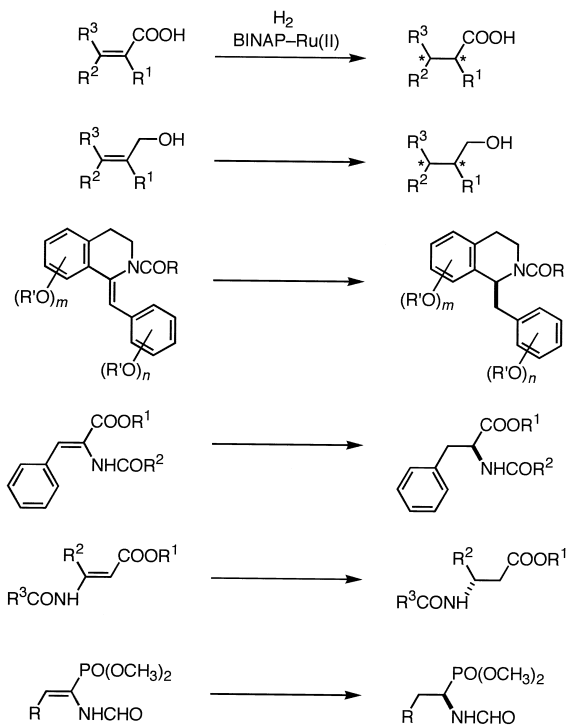
195

Figure 9. Asymmetric hydrogenation of functionalized olefins catalyzed by (*S*)-BINAP–Ru dicarboxylates.
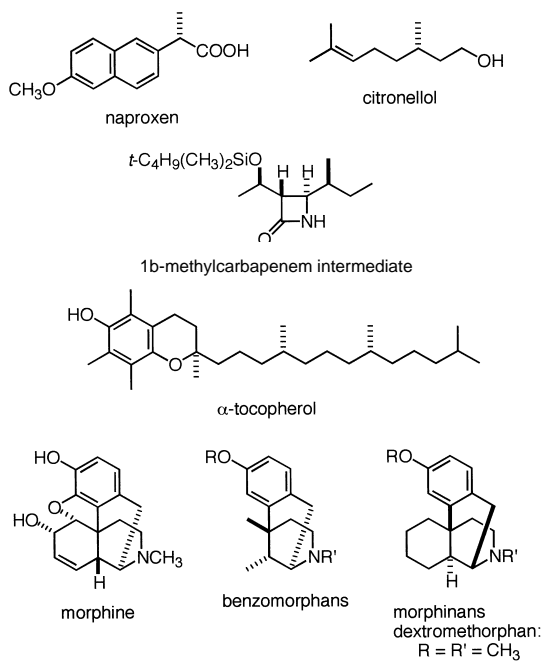

Figure 10. Applications of BINAP–Ru catalyzed hydrogenation of olefins.

196

6,7,10,11-tetrahydrofarnesol produces $(3R,7R)$-hexahydrofarnesol, a C_{15} side chain of α-tocopherol (vitamin E) and a part of vitamin K_1. The hydrogenation of an allylic alcohol possessing a chiral azetidinone unit gives a 1β-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 Figure 11. The halogen-containing BINAP–Ru(II) complexes (oligomers)[50], but not the diacetate complexes, are efficient cata-
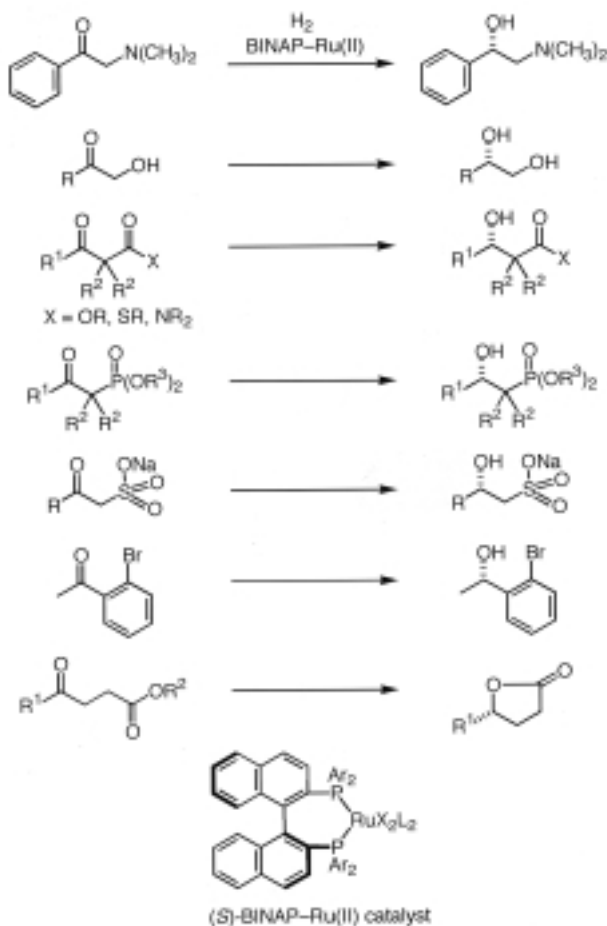

Figure 11. Asymmetric hydrogenation of functionalized ketones catalyzed by (S)-BINAP–Ru dihalide complexes (X = halogen). Photo: major contributors (from the left, H. Takaya, M. Kitamura, and T. Ohkuma).

lysts for the asymmetric hydrogenation of a range of functionalized ketones, wherein coordinative nitrogen, oxygen, and halogen atoms near C=O functions direct the reactivity and stereochemical outcome in an absolute sense[51]. 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 be performed normally in alcohols with up to 50% substrate concentration under 4–100 atm at room temperature with an S/C ratio of up to 10 000 on any scale even using >100 kg of the substrate. Figure 12 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./Daiichi 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].
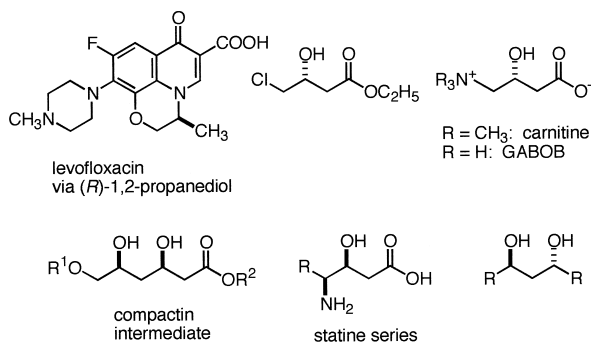

Figure 12. Applications of BINAP–Ru catalyzed hydrogenation of ketones.

Racemic β-keto esters with a configurationally labile α-stereogenic center, undergoing *in situ* stereoinversion, can be transformed into a single stereoisomer, out of the four stereoisomers, with high stereoselectivity, as illustrated in Figure 13[54]. This dynamic kinetic resolution[55] has been used for the synthesis of various biologically important compounds such as threonine, L-DOPS[52], phosphothreonine[56], and fosfomycin[57]. Its utility was highlighted by the industrial synthesis of carbapenem antibiotics at Takasago International Co. (Figure 14). The requisite chiral 4-acetoxyazetidinone is prepared by the (*R*)-BINAP–Ru catalyzed hydrogenation of racemic methyl α-(benzamidomethyl)acetoacetate in dichloromethane giving the 2*S*,3*R* hydroxy ester with 94:6 erythro:threo diastereoselectivity[58] and 99.5:0.5 enantioselectivity[54a]. Quantitative analysis[54] indicates that the 2*S* substrate is hydrogenated 15 times faster than the *R* enantiomer, and the slow-reacting *R* isomer is inverted to the 2*S* enantiomer 92 times easier than it is hydrogenated. The extent of the BINAP catalyst-based asymmetric induction is calcu-
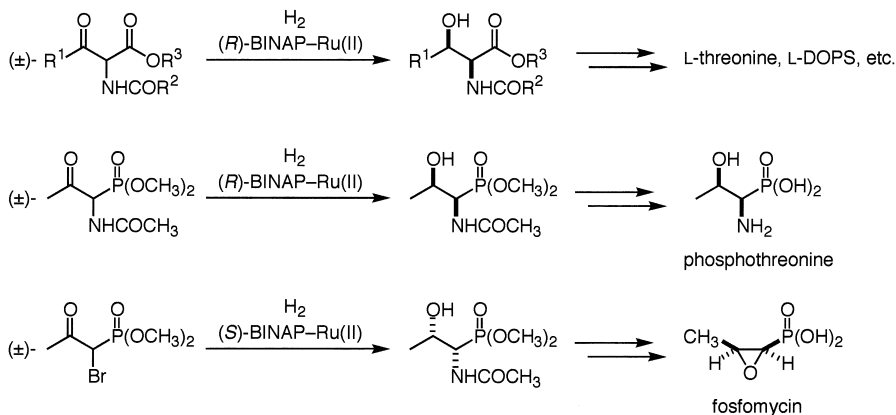
198

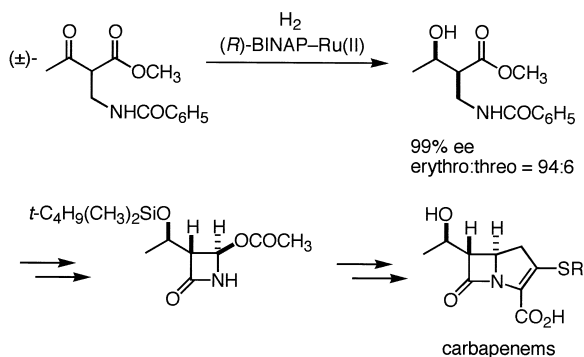*Figure 13.* Asymmetric hydrogenation via dynamic kinetic resolution.

Figure 14. Stereoselective synthesis of carbapenem antibiotics.

lated to be 104 in favor of the $3R$ isomer, whereas the substrate-based asymmetric induction is 9 in favor of the $C(2)/C(3)$ erythro stereochemistry. The volume of the hydrogenation reactor shown in Figure 15 is 13 m³.

β-Keto esters are the best substrates for the Ru catalyzed asymmetric hydrogenation leading to the β-hydroxy esters in >98% ee[59]. Figure 16 illustrates the mechanistic model. The halide ligand in the Ru complex, generating a strong acid and a RuHCl species by the action of H_2, is important to facilitate the hydride transfer from Ru to the carbonyl carbon[55]. 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 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 Figure 11) exerts a pivotal function in the acceleration of hydrogenation as well. Thus, β-keto
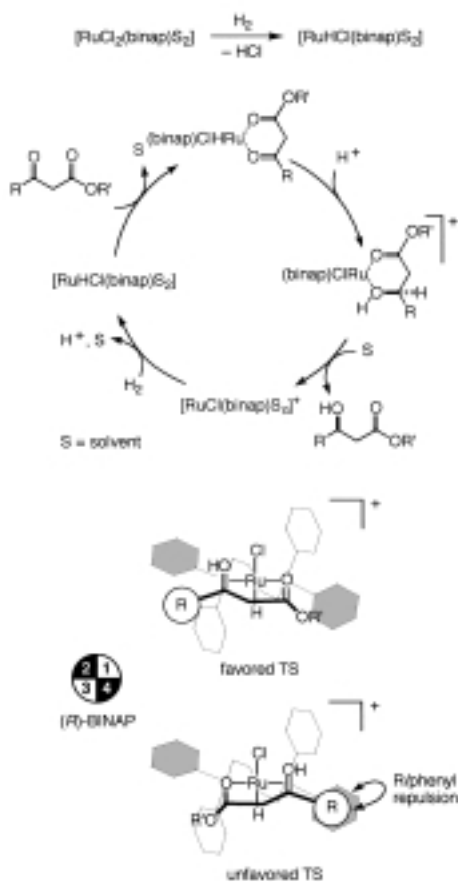
Figure 16. Mechanism of (*R*)-BINAP–Ru catalyzed hydrogenation of β-keto esters.

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.

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 developed largely by H. C. Brown (1979 Nobel laureate). Chemoselective reduction of a C=O function in the presence of a C=C group has been best effected by the stoichiometric $NaBH_4$ reagent[60]. Diastereoselective reduction of ketones has frequently been achieved by Selectrides[61]. Enantioselective reduction of achiral ketones are effected by chiral stoichiometric reagents including BINAL-H[62], DIP chloride[63], and Alpine-borane[64] or by the Corey–Bakshi–Shibata (CBS) method combining B_2H_6 or catecholborane and a chiral oxazaborolidine catalyst[65]. Until very recently, these types of selective C=O reductions were not generally achievable 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 $RuCl_2$(phosphine)$_2$(diamine) complex and an alkaline base provided a general solution to this long-standing problem[67]. The use of appropriate chiral diphosphines and chiral diamines allows asymmetric hydrogenation of simple ketones which lack any Lewis-basic functionality capable of interacting 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 Figure 17, the newly devised BINAP/diamine complex catalyzes rapid, productive and highly enantioselective hydrogenation of a range of aromatic, hetero-aromatic, and olefinic ketones in 2-propanol containing KO-t-C_4H_9 or KOH[68–70]. Among various complexes, $RuCl_2$(xylbinap)(daipen)[71] is particularly effective. For example, acetophenone and its derivatives are hydrogenated with S/C of up to 100 000 giving 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 coexisting C=C linkage[73,74]. Olefinic ketones, either conjugated or nonconjugated, can be converted to olefinic alcohols selectively. The hydrogenation tolerates various functionalities including F, Cl, Br, I, CF_3, OCH_3, $OCH_2C_6H_5$, $COOCH(CH_3)_2$, 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 $RuCl_2$(PAr$_3$)$_2$($NH_2CH_2CH_2$-NH_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 configurationally labile ketones allows for the
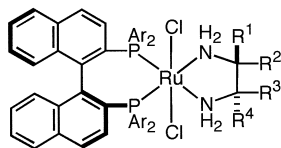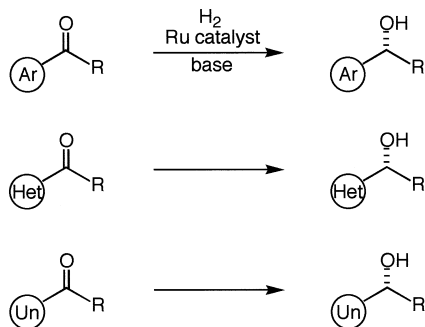
(S)-BINAP/(S)-diamine–Ru(II) catalyst

(S)-BINAP: Ar = C_6H_5

(S)-TolBINAP: Ar = $4\text{-}CH_3C_6H_4$

(S)-XylBINAP: Ar = $3,5\text{-}(CH_3)_2C_6H_3$

(S,S)-DPEN: $R^1 = R^4 = C_6H_5$; $R^2 = R^3 = H$

(S)-DAIPEN : $R^1 = R^2 = 4\text{-}CH_3OC_6H_4$; $R^3 = H$; $R^4 = (CH_3)_2CH$

Figure 17. General asymmetric hydrogenation of simple ketones. Ar = aryl, Het = hetero-aryl, Un = alkenyl.

dynamic kinetic discrimination of diastereomers, epimers, and enantio-mers[76–78], effecting 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 diphosphine/diamine Ru com-plexes effect enantioselective hydrogenation of certain amino or amido keto-nes via a non-chelate mechanism without interaction between Ru and nitro-gen or oxygen[78]. This method has been applied to the asymmetric syn-thesis of various important pharmaceuticals, including (R)-denopamine, a β_1-receptor agonist, the antidepressant (R)-fluoxetine, the antipsychotic BMS 181100, and (S)-duloxetine which is a potent inhibitor of serotonin and no-repinephrine uptake carriers (Figure 18). Benzophenones can be hydroge-nated to benzhydrols with an S/C ratio of up to 20 000 without over-reduc-tion[79]. Enantioselective hydrogenation of certain *ortho*-substituted ben-zophenones leads to the unsymmetrically substituted benzhydrols with high ee, allowing 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 hy-drogenation of α,β-unsaturated ketones to chiral allylic alcohols of high
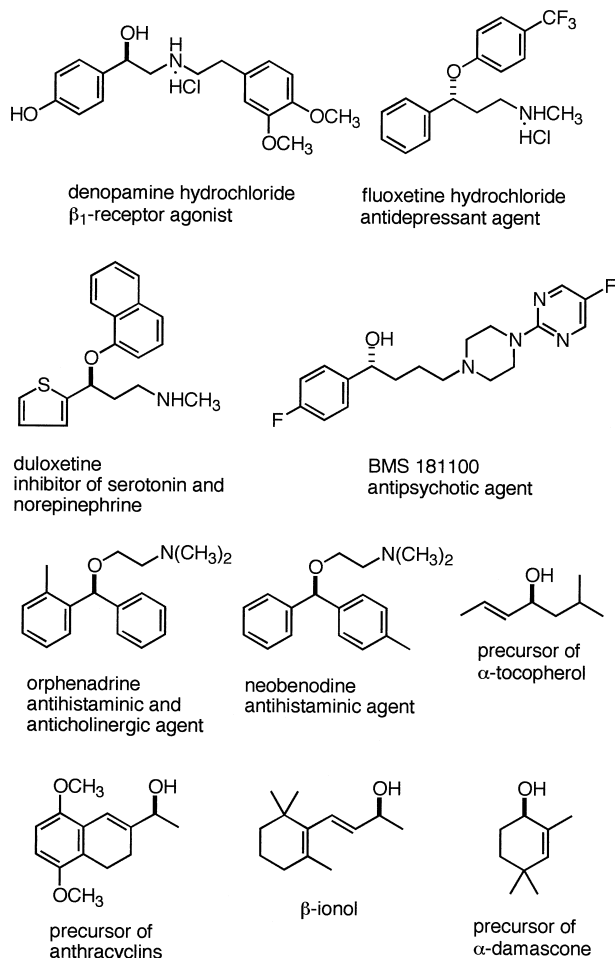
Figure 18. Application of asymmetric hydrogenation of simple ketones.

enantiomeric purity[72–74]. The selectivity profile is in sharp contrast to that observed with the diamine-free BINAP–Ru complex, efficiently catalyzing asymmetric hydrogenation of allylic alcohols (Figure 9). Its utility has been demonstrated by the synthesis of intermediates of an α-tocopherol side chain and anthracyclines as well as β-ionol (Figure 18)[72,73]. The asymmetric hydrogenation shown in Figure 17 is generally achieved by the combined use of an (*S*)-BINAP ligand and an (*S*)-1,2-diamine (or *R* and *R*). This is also the case for the reaction of *s*-cis exocyclic enones, such as (*R*)-pulegone. However, asymmetric hydrogenation of 2,4,4-trimethyl-2-cyclohexenone was effected best with RuCl$_2$[(*S*)-tolbinap][(*R,R*)-dpen][74,80]. The cyclic allyl alcohol obtained in 96% ee (Figure 18) can be converted to a series of carotenoid-derived odorants and bioactive terpenes, such as α-damascone. The *R* or *S* alcohols with ee as high as 95% can be obtained even with a racemic TolBINAP–RuCl$_2$ complex in the presence of (*R,R*)- or (*S,S*)-DPEN via asymmetric activation[80–82]. In this case, the highly enantioselective hydrogenation cata-

lyzed by the (S)-diphosphine/(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[83].

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 KO-t-C$_4$H$_9$ (5.6 g) in 2-propanol (1.5 L) (30% w/v substrate concentration) was stirred under 45 atm H$_2$ at 30 °C for 48 h, the R alcohol was obtained with 80% ee and 100% yield[71,84]. Under such conditions, the turnover number was greater than 2 400 000, while the turnover frequency at 30% conversion was 228 000 h^{-1} or 63 s^{-1}.

This high rate and chemoselectivity for the C=O function are due to the nonclassical metal–ligand bifunctional mechanism (Figure 19)[68,70]. The hydrogenation involves a metal hydride intermediate. Hydride transfer from the metal to the carbonyl carbon has been considered to occur via a 2 + 2 mechanism. This reaction involves a Ru hydride species possessing an NH$_2$ li-
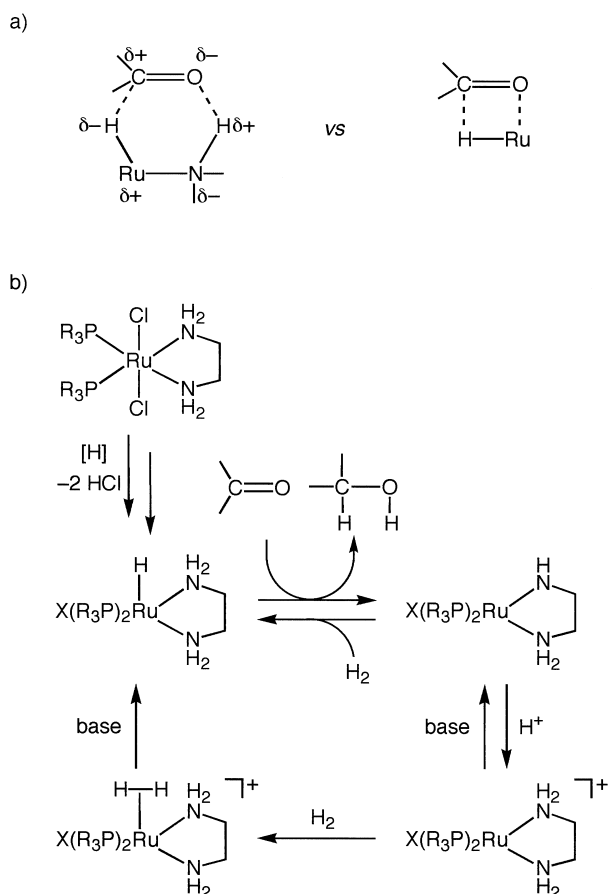

Figure 19. a) Nonclassical metal–ligand bifunctional mechanism and conventional 2 + 2 mechanism. b) Catalytic cycle of hydrogenation of ketones with a RuCl$_2$(PR$_3$)$_2$(NH$_2$CH$_2$CH$_2$-NH$_2$)/strong base combined system in 2-propanol. X = H, OR, etc.

gand, 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 forming a metal alkoxide (Figure 19a). 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 19b. The 18e RuH species reduces the ketone substrate via the pericyclic mechanism and the formal 16e Ru amide reacts directly with H_2 in a 2 + 2 manner or by a stepwise mechanism assisted by an alcohol and a base, giving back the reducing RuH complex[85]. The reducing activity of the RuH species is generated by the hydrogen-bonding NH_2 end in the diamine ligand that 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[86]. Recently we found that RuCl[(*S,S*)-YCH-$(C_6H_5)CH(C_6H_5)NH_2](\eta^6$-arene) (Y = O, NTs) or their analogues catalyze asymmetric transfer hydrogenation of aromatic and acetylenic carbonyl compounds using a 2-propanol/alkaline base system to give the corresponding *S* chiral alcohols of high enantiomeric purity, as generalized in Figure 20[87,88]. A formic acid/triethylamine mixture often serves as a better reducing agent. Certain imines are also reduced enantioselectively by this method. The detailed experimental[89] and theoretical analyses[90] revealed that the transfer hydrogenation of carbonyl compounds with 2-propanol proceeds via a coordinatively saturated 18e complex, RuH[(*S,S*)-YCH(C_6H_5)CH-$(C_6H_5)NH_2](\eta^6$-arene), as illustrated in Figure 21. The metal–ligand bifunctional mechanism allows for simultaneous delivery of the Ru–H and N–H to the C=O function via a six-membered pericyclic TS, giving an *S* alcohol and Ru[(*S,S*)-YCH(C_6H_5)CH(C_6H_5)NH](η^6-arene). The latter 16e Ru amide complex dehydrogenates 2-propanol to regenerate the Ru hydride species[86,91].

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 interdisciplinary 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.

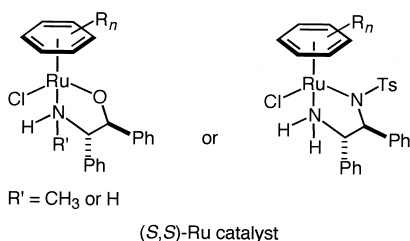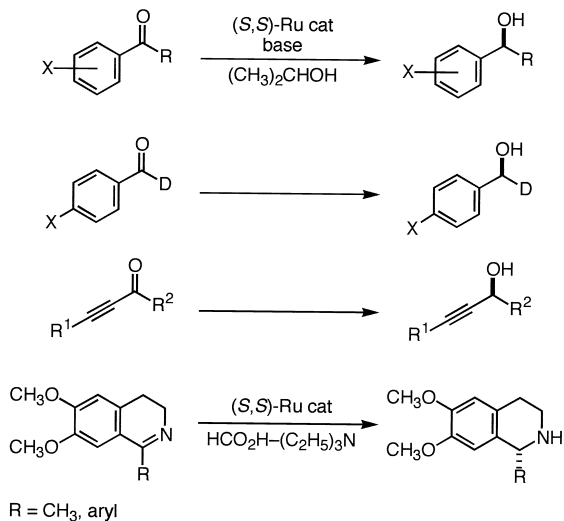In the mid-1980s, we established the long-sought after three-component

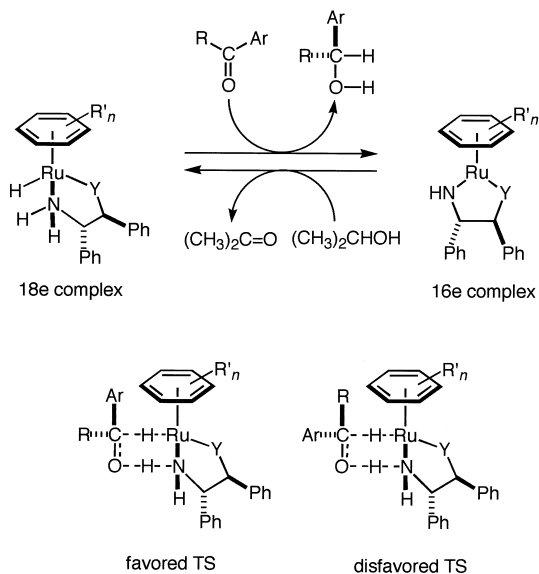*Figure 20.* Asymmetric transfer hydrogenation of carbonyl compounds and imines catalyzed by chiral Ru complexes.

Figure 21. Metal–ligand bifunctional mechanism in asymmetric transfer hydrogenation catalyzed by RuH[(S,S)-YCH(C_6H_5)CH(C_6H_5)NH$_2$](η^6-arene). R = alkyl or D; Y = O or NTs.

206

coupling synthesis of prostaglandins (PGs) illustrated in Figure 22[92]. The five-membered unit could be combined with the two C_7 and C_8 side chain 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 multi-kilogram scale by kinetic resolution of the racemate by BINAP–Ru catalyzed hydrogenation[43]. The BINAL–H reagent is useful for asymmetric synthesis of the lower side-chain block[93,94]. This straightforward procedure is useful for the synthesis of not only naturally occurring PGs but also their artificial analogues[95].

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. Långström (Uppsala University)[96,97]. After a long investigation, (15*R*)-TIC, a PGI$_2$-type carboxylic acid, was found to show strong, selective binding in the central nervous system, thereby identifying the novel IP$_2$ receptor (Figure 23). Interestingly, this compound has the unnatural 15*R* configuration, although most biologically active PG derivatives have the natural 15*S* configuration. This discovery was made by an in vitro study using frozen sections of rat brain and (15*R*)-[^{3}H]TIC as a probe[98]. However, this radioactive probe is not appropriate for studies on living monkey or human brain, since β$^-$ particles emitted from ^{3}H can not penetrate tissues. Incorporation of ^{11}C, a positron emitter having 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 (β$^+$) interact with free electrons in biological materials producing γ rays that can penetrate tissues
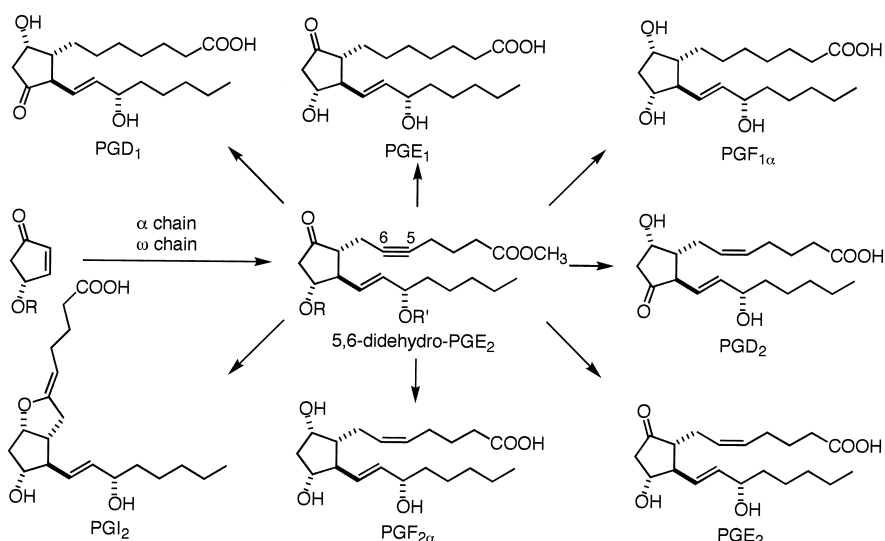

Figure 22. Three-component synthesis of prostaglandins. α chain = $ICH_2C \equiv C(CH_2)_3$-$COOCH_3$; ω chain = (*E,S*)-LiCH=CHCH(OR')(CH$_2$)$_4$CH$_3$.
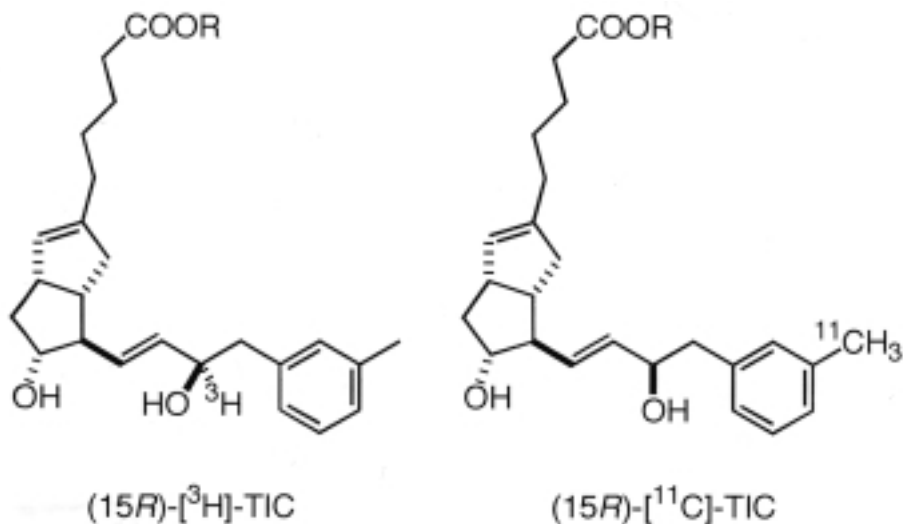
Figure 23. (15*R*)-TIC (R = H) and the methyl esters (R = CH$_3$) labeled by radioactive nuclides and an interdisciplinary collaborative team (from the left, M. Suzuki, R. Noyori, Y. Watanabe, and B. Långström).

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 (15*R*)-TIC methyl ester, and the total time for synthesis, work-up, 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 (15*R*)-[^{11}C]TIC methyl ester[99].

This technology was then transferred to the PET Center at Uppsala. A very dedicated colleague in our team, Suzuki, volunteered to test this new artificial compound on himself. After being carefully examined, (15*R*)-[^{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 24 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, (15*R*)-TIC and its analogues are expected to have effects
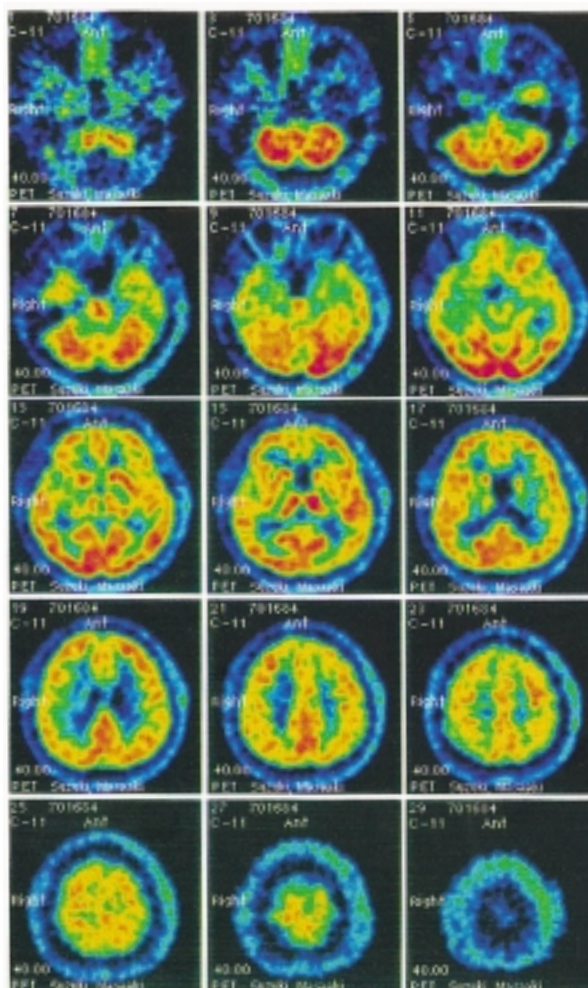
Figure 24. The uptake of (15*R*)-[^{11}C]-TIC in the human brain. The PET images of 18 horizontal slices from the lower to the upper portions of the brain (volunteer: M. Suzuki; June 13, 2000. PET Center of Uppsala University).

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 (15*R*)-TIC effectively protects them against such oxygen toxicity[100]. Similar neuroprotective effects were demonstrated in other *in vitro* experiments using serum deprivation and in *in vivo* studies of ischemic insults with gerbils, rats, and monkeys. Thus, the IP$_2$ receptor is a novel target for developing drugs which may be neuroprotective in brain disorders and neutrodegenerative diseases.

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 exist. All molecules possess common characteristics,

viz., fixed elemental composition, definite atomic connectivity, a defined relative and absolute stereochemistry, 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[101]. Its utility is obvious, ranging from basic scientific research at a sub-femtomol scale, as in the case of brain research described above, to the industrial production of high-value compounds in multi-thousand 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 still growing rapidly and I am certain that it will play a pivotal role in the development of the life sciences and nano-technology in the 21st century.

REFERENCES

[1] For example, a) M. Gardner, *The New Ambidextrous Universe, 3rd Rev. Ed.*, W. H. Freeman & Co., New York, **1990**; b) E. Heilbronner, J. D. Dunitz, *Reflections on Symmetry*, VHCA–VCH, Basel, Weinheim, **1993**; c) R. Hoffmann, *The Same and Not the Same*, Columbia University Press, New York, **1995**; d) H. Brunner. *Rechts oder links in der Natur und anderswo*, Wiley–VCH, Weinheim, **1999**.

[2] G. Blaschke, H. P. Kraft, K. Fickentscher, F. Köhler, *Arzneim.-Forsch./Drug. Res.* **1979**, *29(II)*, 1640.

[3] This interpretation must be considered carefully, because the *R* enantiomer racemizes *in vivo*.

[4] a) *Chem. Eng. News* **1990**, *68*(12), 26; b) S. Borman, *Chem. Eng. News* **1990**, *68*(28), 9.

[5] S. C. Stinson, *Chem. Eng. News* **1992**. *70*(39), 46.

[6] S. C. Stinson, *Chem. Eng. News* **2001**, *79*(20), 45.

[7] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.

[8] a) H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, 5239; b) H. Nozaki, H. Takaya, S. Moriuti, R. Noyori, *Tetrahedron* **1968**, *24*, 3655.

[9] a) T. Aratani, *Pure Appl. Chem.* **1985**, *57*, 1839; b) T. Aratani in *Comprehensive Asymmetric Catalysis, Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 1451.

[10] a) M. Calvin, *Trans. Faraday Soc.* **1938**, *34*, 1181; b) M. Calvin, *J. Am. Chem. Soc.* **1939**, *61*, 2230.

[11] J. Halpern, J. F. Harrod, B. R. James, *J. Am. Chem. Soc.* **1961**, *83*, 753.

[12] J. F. Young, J. A. Osborn, F. H. Jardine, G. Wilkinson, *Chem. Commun.* **1965**, 131.

[13] S. Akabori, S. Sakurai, Y. Izumi, Y. Fujii, *Nature* **1956**, *178*, 323.

[14] W. S. Knowles, M. J. Sabacky, *Chem. Commun.*, **1968**, 1445.

[15] L. Horner, H. Siegel, H. Büthe, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942.

[16] These achievements were based on the classic work of Mislow and Horner on resolution of chiral tertiary phosphines: a) O. Korpiun, R. A. Lewis, J. Chickos, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4842; b) L. Horner, *Pure Appl. Chem.* **1964**, *9,* 225,

[17] T. P. Dang, H. B. Kagan, *J. Chem. Soc. Chem. Commun.* **1971**, 481.

[18] a) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J. Chem. Soc., Chem. Commun.* **1972**, 10; b) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946; c) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106; d) J. Crosby in *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, Chichester, **1992**, chap 1.

[19] E. J. Corey, R. Noyori, T. K. Schaaf, *J. Am. Chem. Soc.* **1970**, *92*, 2586.

[20] One of the early examples of successful asymmetric catalysis was the Ni-catalyzed hydrovinylation of norbornene: See: B. Bogdanovic, B. Henc, A. Lösler, B.Meister, H. Pauling, G. Wilke, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 954.

[21] R. Noyori, H. Takaya, *Chemica Scripta* **1985**, *25*, 83.

[22] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932.

[23] a) A. Miyashita, H. Takaya, T. Souchi, R. Noyori, *Tetrahedron* **1984**, *40*, 1245; b) K. J. Brown, M. S. Berry, K. C. Waterman, D. Lingenfelter, J. R. Murdoch, *J. Am. Chem. Soc.* **1984**, *106*, 4717.

[24] H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, R. Noyori, *J. Org. Chem.* **1986**, *51*, 629.

[25] For the more recent stereospecific synthesis by Ni-catalyzed coupling between optically pure binaphthol ditriflate and diphenylphosphine, see: D. Cai, J. F. Payack, D. R. Bender, D. L. Hughes, T. R. Verhoeven, P. J. Reider, *Org. Synth.* **1998**, *76*, 6.

[26] K. Toriumi, T. Ito, H. Takaya, T. Souchi, R. Noyori, *Acta Crystallogr. Sect. B*, **1982**, *38*, 807.

[27] a) K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H.

Takaya, A. Miyashita, R. Noyori, *J. Chem. Soc. Chem. Commun.* **1982**, 600; b) K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, S. Otsuka, *J. Am. Chem. Soc.* **1984**, *106*, 5208.

[28] a) S. Akutagawa in *Organic Synthesis in Japan: Past, Present, and Future* (Eds.: R. Noyori, T. Hiraoka, K. Mori, S. Murahashi, T. Onoda, K. Suzuki, O. Yonemitsu), Tokyo Kagaku Dozin, Tokyo, **1992**, p. 75; b) S. Akutagawa in *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, Chichester, **1992**, chap 16.

[29] a) S. Otsuka, K. Tani in *Asymmetric Synthesis Vol. 5* (Ed.: J. D. Morrison), Academic Press, Orlando, **1985**, chap 6; b) S. Otsuka, K. Tani, *Synthesis* **1991**, 665; c) S. Otsuka, *Acta Chem. Scand.* **1996**, *50*, 353.

[30] K. Takabe, T. Yamada, T. Katagiri, J. Tanaka, *Org. Synth.* **1989**. *67*, 48.

[31] M. Yamakawa, R. Noyori, *Organomet.* **1992**, *11*, 3167.

[32] a) R. Noyori, *Chem. Soc. Rev.* **1989**, *18*, 187; b) R. Noyori, *Science* **1990**, *248*, 1194; c) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345; d) R. Noyori, *CHEMTECH* **1992**, *22*, 360; e) R. Noyori, *Tetrahedron* **1994**, *50*, 4259; f) R. Noyori in *(IUPAC) Stereocontrolled Organic Synthesis* (Ed.: B. M. Trost), Blackwell Scientific Publications, Oxford, **1994**, p. 1; g) R. Noyori, *Acta Chem. Scand.* **1996**, *50*, 380.

[33] An early example of phosphine–Ru complex catalyzed hydrogenation: P.S. Hallman, B. R. McGarvey, G. Wilkinson, *J. Chem. Soc. A* **1968**, 3143.

[34] Ru-catalyzed asymmetric hydrogenation of olefins was first achieved using a DIOP–Ru complex: B. R. James, D. K. W. Wang, R. F. Voigt, *J. Chem. Soc., Chem. Commun.* **1975**, 574.

[35] C. R. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 1746.

[36] J. M. Brown, P. A. Chaloner, *J. Am. Chem. Soc.* **1980**, *102*, 3040.

[37] For an exmple of a solution to this problem, see: I. D. Gridnev, N. Higashi, K. Asakura, T. Imamoto, *J. Am. Chem. Soc.* **2000**, *122*, 7183.

[38] R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, H. Takaya, *J. Am. Chem. Soc.* **1986**, *108*, 7117.

[39] a) T. Ohta, H. Takaya, R. Noyori, *Inorg. Chem.* **1988**, *27*, 566; b) M. Kitamura, M. Tokunaga, R. Noyori, *J. Org. Chem.* **1992**, *57*, 4053; c) H. Takaya, T. Ohta, S. Inoue, M. Tokunaga, M. Kitamura, R. Noyori, *Org. Synth.* **1993**, *72*, 74.

[40] a) T. Ohta, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1990**, *31*, 7189; b) M. T. Ashby, J. Halpern, *J. Am. Chem. Soc.* **1991**, *113*, 589.

[41] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174.

[42] H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, R. Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 1596 and 4129.

[43] M. Kitamura, I. Kasahara, K. Manabe, R. Noyori, H. Takaya, *J. Org. Chem.* **1988**, *53*, 708.

[44] a) M. Kitamura, Y. Hsiao, R. Noyori, H. Takaya, *Tetrahedron Lett.* **1987**, *28*, 4829; b) M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, R. Noyori, *J. Org. Chem.* **1994**, *59*, 297.

[45] W. D. Lubell, M. Kitamura, R. Noyori, *Tetrahedron: Asymmetry* **1991**, *2*, 543.

[46] M. Kitamura, M. Yoshimura, M. Tsukamoto, R. Noyori, *Enantiomer* **1996**, *1*, 281.

[47] T. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa, S. Akutagawa, *J. Chem. Soc. Chem. Commun.* **1985**, 922. This was the first use of BINAP in Ru-catalyzed asymmetric hydrogenation.

[48] M. Kitamura, K. Nagai, Y. Hsiao, R. Noyori, *Tetrahedron Lett.* **1990**, *31*, 549.

[49] For other synthetic applications, see reviews: a) G. M. Ramos Tombo, G. Belluš, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1193; b) A. Börner, J. Holz in *Transition Metals for Organic Synthesis, Vol. 2* (Eds.: M. Beller, C. Bolm), Wiley–VCH, Weinheim, **1998**, p. 3; c) J. M. Brown in *Comprehensive Asymmetric Catalysis, Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 121; d) T. Ohkuma, M. Kitamura, R. Noyori in *Catalytic Asymmetric Synthesis, 2nd Ed.* (Ed.: I. Ojima), Wiley–VCH, New York, **2000**, p. 1.

[50] a) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Tetrahedron Lett.* **1991**, *32*, 4163; b) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Org. Synth.* **1993**, *71*, 1; c) K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem.* **1994**, *59*, 3064. The halogen-containing Ru complexes are also effective for asymmetric hydrogenation of various functionalized olefins.

[51] a) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 629; b) K. Mashima, K. Kusano, T. Ohta, R. Noyori, H. Takaya, *J. Chem. Soc. Chem. Commun.* **1989**, 1208; c) T. Ohkuma, M. Kitamura, R. Noyori, *Tetrahedron Lett.* **1990**, *31*, 5509.

[52] M. Kitamura, T. Ohkuma, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1988**, *29*, 1555.

[53] T. Nishi, M. Kitamura, T. Ohkuma, R. Noyori, *Tetrahedron Lett.* **1988**, *29*, 6327.

[54] a) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, H. Kumobayashi, *J. Am. Chem. Soc.* **1989**, *111*, 9134; b) M. Kitamura, T. Ohkuma, M. Tokunaga, R. Noyori, *Tetrahedron: Asymmetry* **1990**, *1*, 1.

[55] a) M. Kitamura, M. Tokunaga, R. Noyori, *J. Am. Chem. Soc.* **1993**, *115*, 144; b) M. Kitamura, M. Tokunaga, R. Noyori, *Tetrahedron* **1993**, *49*, 1853; c) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

[56] M. Kitamura, M. Tokunaga, T. Pham, W. D. Lubell, R. Noyori, *Tetrahedron Lett.* **1995**, *36*, 5769.

[57] M. Kitamura, M. Tokunaga, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2931.

[58] For the threo/erythro nomenclature, see: R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1981**, *103*, 2106.

[59] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, *109*, 5856.

[60] a) H. C. Brown, H. I. Schlesinger, I. Sheft, D. M. Ritter, *J. Am. Chem. Soc.* **1953**, *75*, 192; b) H. I. Schlesinger, H. C. Brown, A. E. Finholt, *J. Am. Chem. Soc.* **1953**, *75*, 205. Reviews: c) H. C. Brown, S. Krishnamurthy, *Tetrahedron* **1979**, *35*, 567; d) H. C. Brown, P. V. Ramachandran in *Reductions in Organic Synthesis: Recent Advances and Practical Applications (ACS symposium series 641)* (Ed.: A. F. Abdel-Magid), American Chemical Society, Washington, DC, **1996**, chap 1.

[61] a) H. C. Brown, S. Krishnamurthy, *J. Am. Chem. Soc.* **1972**, *94*, 7159; b) S. Krishnamurthy, H. C. Brown, *J. Am. Chem. Soc.* **1976**, *98*, 3383.

[62] a) R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6709; b) R. Noyori, I. Tomino, M. Yamada, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6717.

[63] P. V. Ramachandran, H. C. Brown in *Reductions in Organic Synthesis: Recent Advances and Practical Applications (ACS symposium series 641)* (Ed.: A. F. Abdel-Magid), American Chemical Society, Washington, DC, **1996**, chap 5.

[64] M. M. Midland, *Chem. Rev.* **1989**, *89*, 1553.

[65] E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.

[66] For early efforts, see: a) J. Solodar, *CHEMTECH* **1975**, *5*, 421; b) T. Hayashi, T. Mise, M. Kumada, *Tetrahedron Lett.* **1976**, 4351; c) S. Törös, B. Heil, L. Kollár, L. Markó, *J. Organomet. Chem.* **1980**, *197*, 85; d) J. Bakos, I. Tóth, B. Heil, L. Markó, *J. Organomet. Chem.* **1985**, *279*, 23; e) X. Zhang, T. Taketomi, T. Yoshizumi, H. Kumobayashi, S. Akutagawa, K. Mashima, H. Takaya, *J. Am. Chem. Soc.* **1993**, *115*, 3318. See also: f) F. Robin, F. Mercier, L. Ricard, F. Mathey, M. Spagnol, *Chem. Eur. J.* **1997**, *3*, 1365; g) U. Nagel, C. Roller, *Z. Naturforsch., Ser. B* **1998**, *53*, 267; h) Q. Jiang, Y. Jiang, D. Xiao, P. Cao, X. Zhang, *Angew. Chem. Int. Ed.* **1998**, *37*, 1100; i) P. Cao, X. Zhang, *J. Org. Chem.* **1999**, *64*, 2127. Heterogeneous hydrogenation, see: j) T. Osawa, A. Tai, Y. Imachi, S. Takasaki in *Chiral Reactions in Heterogeneous Catalysis* (Eds.: G. Jannes, V. Dubois), Plenum Press, New York, **1995**, p. 75; k) T. Harada, T. Osawa in *Chiral Reactions in Heterogeneous Catalysis* (Eds.: G. Jannes, V. Dubois), Plenum Press, New York, **1995**, p. 83.

[67] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675.

[68] R. Noyori, T. Ohkuma, *Angew. Chem. Int. Ed.* **2001**, *40*, 40.

[69] R. Noyori, T. Ohkuma, *Pure Appl. Chem.* **1999**, *71*, 1493.

[70] R. Noyori, M. Koizumi, D. Ishii, T. Ohkuma, *Pure Appl. Chem.* **2001**, *73*, 227.

[71] Abbreviations: TolBINAP = 2,2'-Bis(di-4-tolylphosphino)-1,1'-binaphthyl. XylBINAP = 2,2'-Bis(di-3,5-xylylphosphino)-1,1'-binaphthyl. DPEN = 1,2-Diphenylethylenediamine. DAIPEN = 1,1-Di-4-anisyl-2-isopropyl-1,2-ethylenediamine.

[72] T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529.

[73] T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 10417.

[74] T. Ohkuma, H. Ikehira, T. Ikariya, R. Noyori, *Synlett* **1997**, 467.

[75] T. Ohkuma, M. Koizumi, M. Yoshida, R. Noyori, *Org. Lett.* **2000**, *2*, 1749.

[76] T. Ohkuma, H. Ooka, M. Yamakawa, T. Ikariya, R. Noyori, *J. Org. Chem.* **1996**, *61*, 4872.

[77] T. Matsumoto, T. Murayama, S. Mitsuhashi, T. Miura, *Tetrahedron Lett.* **1999**, *40*, 5043.

[78] T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 6510.

[79] T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *2*, 659.

[80] T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 1086.

[81] T. Ohkuma, H. Takeno, Y. Honda, R. Noyori, *Adv. Synth. Catal.* **2001**, *343*, 369.

[82] Review: K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud, *Angew. Chem. Int. Ed.* **2000**, *39*, 3532. See also: K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem. Int. Ed.* **1999**, *38*, 495; K. Mikami, T. Korenaga, T. Ohkuma, R. Noyori, *Angew. Chem. Int. Ed.* **2000**, *39*, 3707.

[83] Non-linear effects in catalysis should be investigated carefully because of the homochiral and heterochiral interaction of the chiral species present in the catalytic system. For reviews, see: a) R. Noyori, S. Suga, H. Oka, M. Kitamura, *Chem. Rec.* **2001**, *1*, 85; b) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2922; c) D. R. Fenwick, H. B. Kagan, *Top. Stereochem.* **1999**, *22*, 257.

[84] H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed.* **1998**, *37*, 1703.

[85] The ketone substrate reacts in an outer sphere of the coordinatively saturated 18e 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. Abdur-Rashid, M. Faatz, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2001**, *123*, 7473; b) R. Hartmann, P. Chen, *Angew. Chem. Int. Ed.* **2001**, *40*, 3581.

[86] R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931.

[87] R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97.

[88] a) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738; b) I. Yamada, R. Noyori, *Org. Lett.* **2000**, *2*, 3425.

[89] K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285.

[90] a) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466; b) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580.

[91] M. Yamakawa, I. Yamada, R. Noyori, *Angew. Chem. Int. Ed.* **2001**, *40*, 2818.

[92] a) M. Suzuki, A. Yanagisawa, R. Noyori, *J. Am. Chem. Soc.* **1985**, *107*, 3348; b) M. Suzuki, A. Yanagisawa, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 4718; c) M. Suzuki, Y. Morita, H. Koyano, M. Koga, R. Noyori, *Tetrahedron* **1990**, *46*, 4809.

[93] M. Suzuki, H. Koyano, Y. Morita, R. Noyori, *Synlett* **1989**, 22.

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

[95] a) R. Noyori, M. Suzuki, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847; b) R. Noyori, M. Suzuki, *Chemtracts—Org. Chem.* **1990**, *3*, 173; c) R. Noyori, M. Suzuki, *Science* **1993**, *259*, 44.

[96] a) M. Suzuki, K. Kato, R. Noyori, Yu. Watanabe, H. Takechi, K. Matsumura, B. Långström, Y. Watanabe, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 334; b) H. Takechi, K. Matsumura, Yu. Watanabe, K. Kato, R. Noyori, M. Suzuki, Y. Watanabe, *J. Biol. Chem.* **1996**, *271*, 5901.

[97] Account: M. Suzuki, R. Noyori, B. Långström, Y. Watanabe, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1053.

[98] Yu. Watanabe, K. Matsumura, H. Takechi, K. Kato, H. Morii, M. Björkman, B. Långström, R. Noyori, M. Suzuki, Y. Watanabe, *J. Neurochem.* **1999**, *72*, 2583.

[99] a) M. Suzuki, H. Doi, M. Björkman, Y. Andersson, B. Långström, Y. Watanabe, R. Noyori, *Chem. Eur. J.* **1997**, *3*, 2039; b) M. Suzuki, H. Doi, K. Kato, M. Björkman, B. Långström, Y. Watanabe, R. Noyori, *Tetrahedron* **2000**, *56*, 8263.

[100] T. Satoh, Y. Ishikawa, Y. Kataoka, Y. Cui, H. Yanase, K. Kato, Yu. Watanabe, K. Nakadate, K. Matsumura, H. Hatanaka, K. Kataoka, R. Noyori, M. Suzuki, Y. Watanabe, *Eur. J. Neurosci.* **1999**, *11*, 3115.

[101] R. Noyori, S. Hashiguchi, T. Yamano in *Applied Homogeneous Catalysis by Organometallic Complexes, 2nd ed.* (Eds.: B. Cornils, W. A. Hermann), VCH–Wiley, Weinheim, in press.