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Discoveries of the Catalysis of Asymmetric Isomerization of Allylamines and its Significance in Science and Industry*

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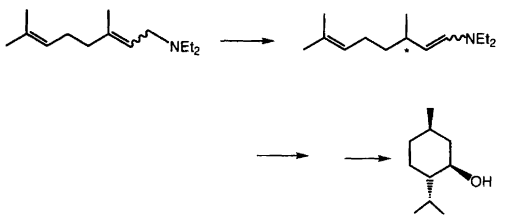
A short historical account is given on the discoveries of Rh^{I}-BINAP-catalyzed asymmetric isomerization of allylamines. The catalysis provides a facile means of making numerous chiral fragrant molecules, stimulating chemical science and culture.

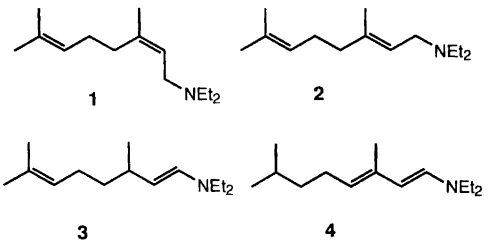
To do or not to do

One day in the mid-seventies, Dr. Komatsu, who was then the research director of Takasago Perfumery Co., accompanied by Professor Emeritus Nozoe, paid a visit to my office in Osaka University. A few weeks later I found myself in discussion with Takasago's chemists, Dr. Akutagawa, Dr. Kumobayashi *et al.* about their new research projects. One of their new research proposals was fantastic, a new (−)-menthol synthesis based on an unknown asymmetric isomerization of an appropriate allylamine to an optically active enamine [eqn. (1)].



(1)

There were industrial as well as scientific incentives to exploit catalytic enantioselective isomerization of allylamines **1** and **2**. Firstly, the starting materials (*Z*)-**1** and (*E*)-allylamine **2** can be produced in quantity.[1] Lithium-catalyzed telomerization of isoprene with a secondary amine as the telomer gives **1** with reasonable selectivity (~92%),[1] one of the rare examples of formation of the natural isoprenoid skeleton directly from isoprene. The addition reaction of myrcene and dialkylamine can be effected with Li or BuLi producing **2** almost quantitatively.[2] Secondly, the product enamine **3** can be hydrolyzed to the corresponding optically active aldehyde without racemization. Thus, the enantioselective isomerization of prochiral allylamines of type **1** or **2**, once achieved, promised successful production of chiral aliphatic chains with a terminal aldehyde group, a challenging target in the field of synthetic chemistry. There were no precedents for this type of catalytic reaction.[3]



Requirements to achieve the enantioselective allylic hydrogen migration appeared to be formidable. (*1*) Excellent enantioface recognition at C3 is necessary, yet there is only a small stereochemical difference between the enantiofaces at C3. (*2*) Although the catalysis is a kinetic phenomenon, the products obtained with active catalysts generally reflect thermodynamic control implying effective reversibility of the reaction steps involved. Migration of a multi-substituted inner double bond to the less-substituted terminal position requires product stabilization either by the terminal functional group or through coordination to a metal (see, for example, the hydrozirconation reaction[4]). (*3*) Substrates **1** and **2** are trisubstituted olefins. Most of the known catalysts appeared not to be very active towards those olefins.[5–7] Moreover, the two double bonds in these substrates pose a problem of chemoselectivity. Conventionally, allylic migration is effected with various bases. Isomerization of **1** or **2** with strong bases such as NaH–ethylenediamine

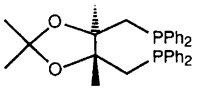
* Contribution presented at the Nobel Symposium on *Catalytic Asymmetric Synthesis*, September 3–7, 1995, Tammsvik, Bro, Sweden.

or sodium naphthalenide produces mainly the undesired conjugated dienamine **4**.[8] Will you still try? *Destiny* pushed me – to do!

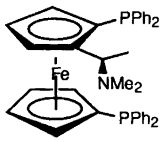
Pilgrimage

A long pilgrimage thus started to search for a catalyst. Cobalt complexes were the first choice, because of the known catalytic activity of low-valent cobalt complexes, such as $CoH(CO)_4$[9,10] for double bond migration. Our experience with butadiene oligomerization also indicated[11–13] the unique ability of cobalt to promote hydrogen migration: whereas low-valent nickel or iron complexes produced cycloadducts, cobalt complexes gave exclusively 3-methylhepta-1,4,6-triene indicative of hydrogen migration.[11]

A preliminary study of the allylic hydrogen migration with cobalt complexes as the catalyst was started by the Takasago group in 1976. Indeed, for the non-stereospecific isomerization, $CoH(N_2)(PPh_3)_3$, a precursor of $CoH(PPh_3)_n (n<3)$, showed catalytic activity. For example, *N,N*-diethylprenylamine (*N,N*-diethyl 3-methyl-2-butenylamine) was isomerized with 1 mol% of the complex (80 °C, 15 h, THF) to give 95% isolated yield of (*E*)-prenylenamine [(*E*)-*N,N*-diethyl-3-methyl-1-(*E*)-butenylamine]. However, the reaction with substrate **1** or **2** gave a lower yield with a considerable amount (~15%) of the undesired dienamine **4**. The asymmetric isomerization of **1** or **2** was attempted employing low-valent cobalt complexes prepared *in situ* from Co^{II} salts, $AlEt_3$ or $AlH(i\text{-}Bu)_2$, and an optically active phosphine (mole ratio 1:3:3). The reaction produced only a very low optical yield (less than 10% ee). Chiral diphosphines such as (+)-DIOP or (*R,S*)-2-(1-aminoethyl)-ferrocenylbis-diphenylphosphine) (BPPFA)[14] gave a somewhat higher optical yield (<25% ee).



(*R,R*)-DIOP



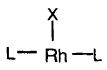
(*S,R*)-BPPFA

Many other chiral ligands were tried in vain. In short, after expending considerable manpower and time (about two years), mainly in the time-consuming preparation of chiral ligands, we came to the conclusion that cobalt compounds would not meet our requirements as to the level of enantioselection. Also the chemical yields were poor (20–50%). The main product was always accompanied by a considerable amount of dienamine **4** and many other unidentifiable products. We ascribed this behavior to the formation of a variety of metal species during the catalysis. It was therefore necessary to find a stereochemically more stable system.

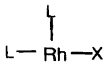
At that time a group led by my associate, Professor Yoshida, was producing a series of low-coordination complexes of Pt^0 and Rh^I.[15–20] Some of them, e.g., $HRhL_n$ [L=PEt_3, $P(i\text{-}Pr)_3$ etc., $n=2$, 3] possess an extraordinary ability to activate small molecules, such as H_2, H_2O, alcohols, etc. In particular, the high activity towards transfer hydrogenation[21] between secondary alcohol and ketone attracted my attention. This catalytic process was in general very clean suggesting that the metal species were stereochemically more stable. This is apparently due to the well known enhanced ligand field stabilization for the second- and third-row transition metals.

In the summer of 1979 two members of the Osaka group (Drs. Tani and Yamagata) began an investigation of the structure of various Rh^I and Rh^{III} compounds containing phosphine ligands. Takasago showed no interest in rhodium catalysis because of the extraordinarily high price of the metal. A series of Rh^I hydride complexes, $HRhL_3$, H_3RhL_2, etc. [L=PEt_3, $P(i\text{-}Pr)_3$, $P(t\text{-}Bu)_3$] showed only low catalytic activity towards the isomerization of **1**. Especially disappointing was the poor performance of $RhH_3[P(i\text{-}Pr)_3]_2$, a precursor of the tri-coordinate species $RhHL_2$. Chloro Rh^I or Rh^{III} complexes such as $RhCl[P(t\text{-}Bu)_3]_3$ or $RhCl(H)_2[P(t\text{-}Bu)_3]_3$ also exhibited only low catalytic isomerization activity.

So far we had seen that Rh^I complexes of monodentate phosphine ligands performed poorly. How about chelating diphosphines? It is well known that square planar d^8 complexes of the type MX_2L_2 (L=monodentate ligand) give rise to *trans-* and *cis-*geometries. It is also possible for tri-coordinated d^8 complexes of type MXL_2 to assume *trans-* and *cis-*geometries (**5a**, **5b**), since the frontier orbital configuration dictates a T-shape as the most stable geometry (Jahn–Teller effect).[22,23] Thus, the use of appropriate chelation should give an opportunity to reduce the number of geometrical isomers in the catalysis. This is also the case for tetra- and penta-coordinations. It was thus of great interest to see the effect of chelation upon the catalysis.



5a

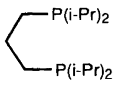


5b

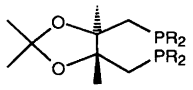
We made two structural types, a neutral Rh^I dimer $[RhCl(DIPHOS)]_2$ [DIPHOS: 1, 2-bis(diphenylphosphino)ethane] and a cationic complex $[Rh\text{-}(COD)(DIPHOS)]^+ClO_4^-$ COD=1,5-cyclooctadiene). The former, a chloride-bridged dimer, was practically inactive in a variety of media, probably due to persistent coordinative saturation. In contrast, the latter was quite active in several solvents. In addition, the catalytic performance was impressively clean: we could detect only the product enamine **3**, the unchanged substrate, and traces of other by-products.[24–27]

By the fall of 1980, we had made the following observations[24] on the isomerization of allylamines **1** and **2**. (i) Among a variety of complex structures, cationic

square planar complexes, $[Rh(DIPHOS)(COD)]^+$ or $[Rh(DIPHOS)(Solv)_n]^+$ (Solv = acetone, THF or methanol) are the most active. (ii) The electronic nature of the diphosphine ligands affects the catalytic activity. Thus, fully alkylated diphosphines such as DIPP and tetraalkyl analogs of DIOP (e.g., *i*-PrDIOP, EtDIOP, CyDIOP, etc.) formed Rh^I complexes of low catalytic activity. In contrast, tetraaryldiphosphines showed better catalytic activity. Accordingly we sought perarylated diphosphines such as biphenyl- or binaphthyl type ligands.



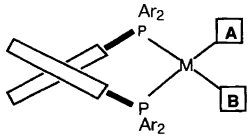
DIPP



(R,R)-RDIOP

What about the chiral structure of the diphosphines? The performance of DIOP already proved to be unsatisfactory for catalytic hydrogenation of some olefins.[28] This was also the case with the asymmetric isomerization of **1** with $[Rh(DIOP)(COD)]^+$ (<26% ee). Only the Rh^ICyDIOP complex gave an exceptionally high optical yield (77% ee). We attributed the poor chiral induction to the conformational flexibility of the seven-membered chelate ring leading to the loss of effective chiral disposition of the four phenyl substituents.

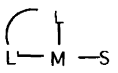
Molecular model studies indicated that BINAP [(+)-or (−)-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl] or its biphenyl analog does not lose the C_2 disposition of the four phenyl groups during the rotation allowed around the C(1)–C(1′) hinge.



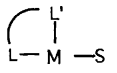
6

The C_2 chelation has further advantages. In a square planar complex **6**, the two sites A and B are of course stereochemically equivalent. A substrate entering site A or B is subject to identical chiral influences. This structure also allows phosphorus site exchange, which might occur via dissociation.

If the chelating ligand lacks C_2 symmetry, the tricoordinated species forms two geometrical isomers. Intramolecular interconversion between **7a** and **7b** could be a low energy process involving a transient species of Y-shape, thus impairing the chiral induction. All these considerations indicated that BINAP or the biphenyl analogue of C_2 symmetry would be ideal for our purpose.



7a



7b

Goddess of fortune

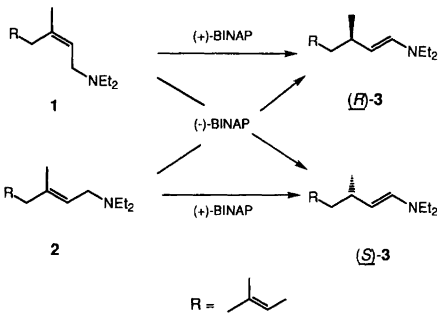
In the late seventies there was a government-supported research project on amino acid synthesis in Japan, and at least four groups were working on the synthesis of BINAP as a new chiral ligand to be utilized in catalytic reactions. A joint effort by the groups at Okazaki (Dr. Takaya) and Nagoya (Prof. Noyori) yielded the first successful synthesis. At my request, made by phone, Dr. Takaya sent me a small amount of the optically active BINAP.

By the fall of 1981, the Osaka group had observed the magnificent performance of Rh^I BINAP complexes, namely virtually perfect enantio-selection (98% ee) and nearly quantitative chemical yields for the isomerization of both (*Z*)- and (*E*)-allylamines. A beautiful stereochemical correlation was soon established between the substrate geometry, product (*E*)-enamine configuration, and the BINAP chirality (Scheme 1).

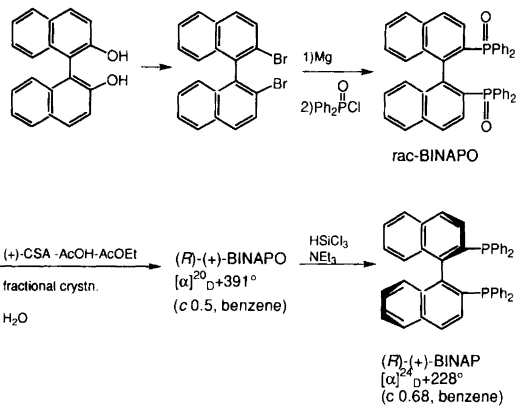
This discovery, an almost unexpected success, induced Takasago to study the economic feasibility of the catalysis. The main problem then was the cost of the catalyst.

Originally optical resolution of racemic BINAP was carried out through complex formation with a chiral Pd^{II} compound.[29,30] The chemists of Takasago were able to find an ingenious method that utilized the basicity of the diphosphine dioxide (BINAPO). Thus, inexpensive chiral acids such as camphorsulfonic acid (CSA) or 2,3-di-*O*-benzoyltartaric acid can be used for the optical resolution of the dioxide (Scheme 2).[31] Deoxygenation of BINAPO can be carried out readily with silyl compounds as usual. (*S*)-(−)-BINAP was thus obtained by employing either (−)-CSA–AcOH or (*R*)-(−)-2,3-di-*O*-benzoyltartaric acid.

Our next objective was to obtain a high turn-over per Rh atom (TN). For laboratory experiments the reasonably stable complex, $[Rh(BINAP)(COD)]^+ClO_4^-$ can be used.[25,27] A more reactive $[Rh(BINAP)(Solv)n]ClO_4$ (Solv = THF, MeOH, acetone; $n = 2$ or 3) is prepared by treating a solution of $[Rh(BINAP)(COD)]ClO_4$ in THF,



Scheme 1.

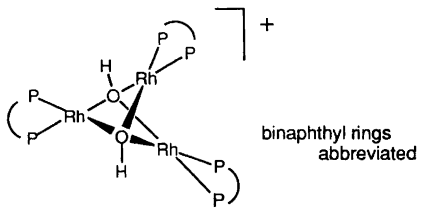


Scheme 2.

MeOH or acetone with dihydrogen (1 atm, ambient temperature) with stirring. The resulting orange solution or suspension (in the case of THF) can be used as a catalyst solution. [Rh(BINAP)(MeOH)2] ClO_4 can be isolated as extremely air-sensitive reddish brown crystals when the solution (methanol) is concentrated and then allowed to stand at low temperature.

Compared with the $[Rh(BINAP)(COD)]^+$ complex, the solvated species $[Rh(BINAP)(Solv)_n]^+$ are in general more reactive and sensitive towards impurities in the substrate and solvent. Consequently the catalyst life is short. Electron-donating substances such as amines, enamines, olefins, and dienes retard the catalytic rate by coordinating strongly to the cationic metal center. This is reflected in the kinetics which shows clearly a trend of product inhibition. Except during the initial stage, the catalytic rate is governed by the rate of product (enamine) replacement with the substrate (allylamine). Therefore removal of amine impurities is important, and this was achieved by distillation of substrate through an efficient column.

In addition, dioxygen and water must be excluded from the reaction system. We found that the reaction of $[Rh(BINAP)(Solv)_n]^+ClO_4^-$ with water led to formation of a reddish-brown crystalline product. This was shown by a single-crystal X-ray analysis to contain a trinuclear monocation with pseudo-D_3 symmetry having triply bridging hydroxo groups on either side of an approximately regular Rh_3 triangle. The cluster is thermally stable and totally inactive, which emphasizes the importance of removal of water.[32]



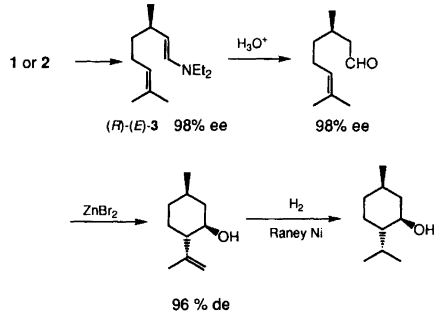
Further, the BINAP ligand was replaced by *p*-TolBINAP, which contains four *p*-tolyl groups in place of the four phenyl substituents. The better solubility of the second generation catalyst complex $[Rh(p\text{-TolBINAP})(COD)]^+ClO_4^-$ allows the simple and effective reactivation of the spent catalyst. The optical yield was almost the same or even slightly better.

Finally, a drastic improvement in catalyst performance was achieved with a bis(diphosphine) complex, $[Rh(p\text{-TolBINAP})_2]^+ClO_4^-$.[33] Since we knew that $[Rh(DIPHOS)_2]^+ClO_4^-$ was inactive for the isomerization of **1** or **2** up to 120 °C, Takasago's discovery that $[Rh(BINAP)_2]^+ClO_4^-$ and $[Rh(p\text{-TolBINAP})_2]^+ClO_4^-$ were quite active at a fairly high temperature (80 °C) came as a surprise.

The molecular structure of $[Rh\{(+)\text{-BINAP}\}_2]^+ClO_4^-$ established by an X-ray analysis, indicated considerable distortion from planarity, the dihedral angle between P1–Rh–P2 and P1′–Rh–P2′ being 6.2(2°). This is due to steric crowding, which also causes elongation of the Rh–P distances [2.368(6)–2.388(6) Å], these being the longest known for the bisphosphine complexes of rhodium(I).[27]

These structural features suggest that intermediates of low coordination such as $[Rh(BINAP)(Substrate)]^+$ or $[Rh(BINAP)(Substrate)(Solv)]^+$ participate in the catalytic cycle. In fact, the stereochemical correlation (Scheme 1) and the degree of optical yield observed with $[Rh(BINAP)_2]^+$ catalysis are identical with that obtained with $[Rh(BINAP)(COD)]^+$, a fact indicative of an identical catalyst structure at the stage where enantioselection is made. The outstandingly long life of the bis-BINAP complex may be accounted for by a *lid-on-off* mechanism: as soon as the substrate is transformed into a product molecule in the coordination sphere of the mono-BINAP Rh species, a free BINAP molecule will immediately displace the product enamine. The quick return to the rather inert bis-BINAP species prevents side reactions that lead to deterioration of the metal species.

After all these efforts Takasago was able to bring on-stream a (−)-menthol plant in 1983 following the reaction sequence of Scheme 3, a process described by Dr. Parshall, Du Pont Central Research, as 'extremely sophisticated'.[34] According to Dr. Akutagawa, who became Research Director after the late Dr. Komatsu, the catalyst recycle can be done many times. Probably more than 400 000 mol of the enamine are produced per



Scheme 3.

mole of Rh^I catalyst.[35] The recycle reduces the catalyst cost to a negligible level. Truly, the Goddess of fortune has smiled: Takasago's output of the optically active enamines is more than 2000 tons per annum, the largest scale process that uses asymmetric catalysis.

The essence of deception

Isaac grew old and dim of sight. He wanted to impart the paternal blessing to the first-born of his twin sons, Esau. Jacob dressed in his brother's robes, with goat skins on his hands and nape to make him hairy like his brother. Deceived by Jacob's smell and feel, lulled by the savory dish Isaac's wife Rebecca made for him, Isaac gave his blessing.

This ancient biblical story of deception, Roald Hoffmann says,[36] has much to do with the way chemicals work and with the strategy of drug design. He describes the way penicillin molecules cheat the bacteria resulting in collapse of their cell walls. To the drugs I would add perfumes, flavors and some agrochemicals.

Insect growth regulators (IGR) with juvenile hormone activity are used to interfere with essential life processes such as metamorphosis and adult emergence. Pest management by IGR requires high potency in pest insects, moderate field stability without undue persistence, selectivity for target pest organisms, etc. Some cases, e.g., natural juvenile hormones of *Hyalophora cecropia* were found to be deficient in all these properties.

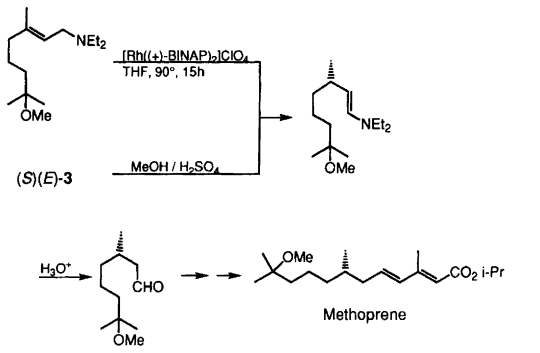
An efficient IGR, which appeared to meet the above requirements, was found by scientists of Zoecon.[37] The compound called 'Methoprene' exhibited remarkable activity, about 100 times that of the natural juvenile hormone for yellow fever mosquito.

The synthetic intermediate, (*S*)-(−)-7-methoxy-3,7-dimethyloctanal must be optically pure. Accordingly a synthesis based on natural citronellal, which in general is not optically pure (Table 1), would not be feasible. However, asymmetric isomerization of 7-methoxygeranylamine effected with $[Rh\{(+)\text{-BINAP}\}_2]^+ + ClO_4^-$ followed by acid hydrolysis (Scheme 4) provides the intermediate with satisfactory optical purity ($[\alpha]_D^{25}$ −11.95° neat; 97.5% ee) and chemical yield (97%). Alternatively methoxylation of (*S*)-citronellal enamine, (*S,E*)-3 (98% ee), with methanol in the presence of 97% sulfuric acid at 0–5 °C followed by hydrolysis gave 7-methoxycitronellal in 79% yield without racemization.

Table 1. Enantiomer composition[a] of natural citronellal.

Source	*S* (−) (%)	*R* (+) (%)
Lemon peel oil	89.0	11.0
Orange peel oil	35.8	64.2
Litsea cubela oi	62.7	37.3
Citronella oil[b]	13.5	86.5
Lemon grass oil	46.8	53.2

[a] Gas chromatography using a chiral stationary phase: heptakis(3-*O*-acetyl-2,6-di-*O*-pentyl)-*b*-dextrin. [b] Ceylon type.



Scheme 4.

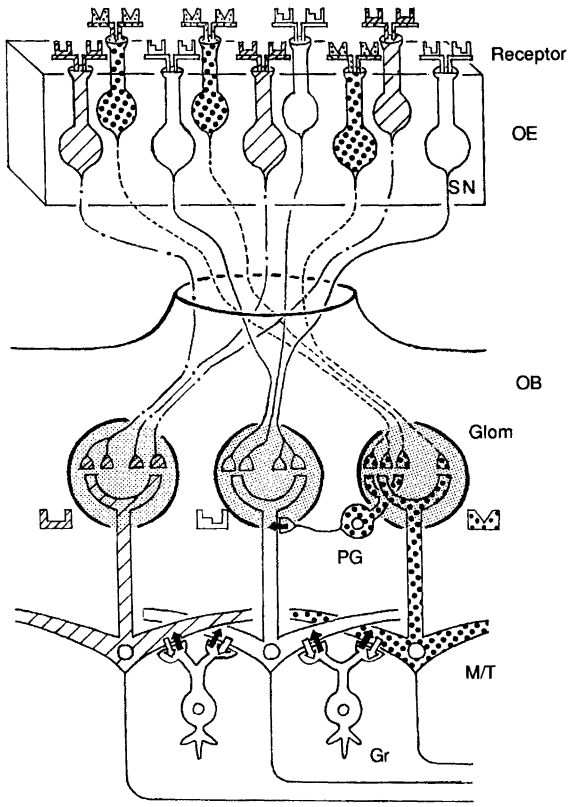


Fig. 1. Mammalian olfactory system. A schematic diagram depicting the convergence onto one glomerulus (Glom) of axons originating from olfactory sensory neurons (SN) expressing the same types of odor recepter. The diagram also contains the lateral inhibitory pathways via local interneurons among mitral tufted (M/T) cells of adjacent glomeruli. Open arrows and filled ones indicate excitatory and inhibitory synapses, respectively. OE, olfactory epithelium; OB, olfactory bulb; PG, periglomerular cell; Gr, granule cell. (Reproduced from the paper by Mori[38b] with permission of the author and of the publisher, Current Biology Ltd., London W1P 6LB, UK.)

The reason for the high activity of some juvenile hormone mimics is not well understood. The flexibility in the receptor fit apparently brings lethal consequence to the target insects.

How do we recognize the enormous variety of odor molecules (more than 400 000)? Figure 1 depicts schemat-

ically a mammalian olfactory system.[38] The olfactory epithelium consists of numerous sensory neurons (SN) each of which carries one or a few types of odor molecule receptor. An axon from the SN leads to a glomerulus (GL) in the main olfactory bulb (OB). The GL, a relay station, is the site of convergence of olfactory axons derived from a number of the same types of receptor. The repertoire of the receptors amounts to about 1000, and the number of GL ranges from 1000 to 3000. Mitral and tufted (M/T) cells, principal neurons in the OB, protrude from the GL. Adjacent M/T cells are connected by an intervening granule cell forming neuronal circuits. In the case of insects, several GLs in the antennal lobe assemble a cluster forming apparently similar neuronal circuits (*vide infra*).

When the receptor is ligated by an odor molecule, an individual GL receives the axonal input and the signal is transferred to the corresponding M/T cells. Then the adjacent M/T cells receive lateral inhibition. This is due to the known ability of M/T cells to form excitatory as well as inhibitory (reciprocal) synapses. When the olfactory receptor system is excited strongly by, e.g., *n*-C_6 and *n*-C_7 aldehyde molecules, the lateral inhibition erases the weaker excitatory responses caused by *n*-C_5 and *n*-C_8 aldehyde molecules reseulting in refinement of olfactory information.

Another feature to be noted is the 'loose fit of the odor receptors'. It may be convenient to define a term 'molecular receptive range' (MRR). Odor molecules that belong to a certain stereochemical range share a particular type of receptor molecule and its sensory neuron. Such flexibility is a logical consequence of the ability of the olfactory recognition system to deal with numerous kinds of odor molecule.

The present asymmetric isomerization catalysis enabled Takasago to prepare a number of enantiomeric or diastereomeric pairs of odor molecules.[39,40] Table 2 compares the odor properties and corresponding threshold values of enantiomeric pairs of citronellal and its derivatives. The two threshold values determined on each enantiomer coincide in some pairs and the odor properties of these enantiomers are rather similar. Apparently these small linear molecules are characterized by large MRR values. Among the compounds listed, citronellyl ethyl ether and citronellenenitrile are not available from natural sources. Namely, the mammalian olfactory system is able to recognize odor molecules unfamiliar to them.

In the case of cyclic compounds, which are sterically more demanding than the linear molecules, a distinct difference can be seen in both the threshold values and odor properties. Table 3[40] compares a few examples. All eight alcohol samples are diastereomeric mixtures (note the C3 configuration). The optically pure diastereomers with the enantiomeric C3 chirality were also prepared to compare their odor properties (Table 4).[40] These data indicate that an equimolar mixture of two diastereomers does not necessarily produce an odor profile to be expected from the simple addition of each odor property.

There is an interesting observation of 'multiple excitation' in the macroglomerular complex (MGC) of an insect antennal lobe.[41–43] In the sphinx moth *Manduca sextra*, the MGC found only in males is specialized for processing information about the conspecific female sex-pheromone blend, which elicits the male mate-seeking behavior. The female pheromone is a blend of two components, (*E,Z*)-10,12-hexadecadienal (bombykal) and (*E,E,Z*)-10,12,14-hexadecatrienal. The axons of the pheromone receptor cells project into the MGC. Simultaneous ligation of bombykal and the trienal to the two receptors on the antennal lobe causes excitation in the MGC. Such a multiple excitation appears to be a device for a particular insect species to achieve effective species discrimination.

Nature often uses a mixture of many kinds of odor molecule to express characteristic smells of a particular

Table 2. Odor profiles and threshold values of citronellal and its derivatives.

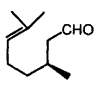
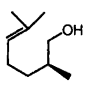
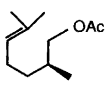
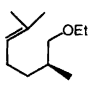
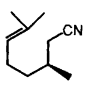
3 *S*-Form	Odor (threshold, ppb)	3 *R*-Form	Odor (threshold, ppb)
	Powerful, fresh, bright clean, herbaceous citrusy (25)		Powerful, fresh, herbaceous-citrusy (25)
	Very fresh light and clean rosy-leafy, petal-like (50)		Slightly oily light rosy–leafy, petal-like odor with irritating top note (50)
	Fresh lime citrus odor with camphoraceous note (250)		Fresh citrus lime odor with dirty aldehyde note (250)
	Clean sweet rosy odor with powerful fresh top note (500)		Fresh rosy odor (500)
	Strong citrus odor with aldehyde note (250)		Fresh mild citrus (100)

Table 3. Odor profiles and threshold values of 1-(2,2,6-trimethycyclohexyl)alkan-3-ols.

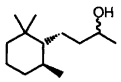
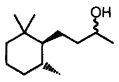
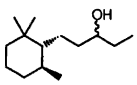
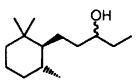
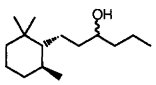
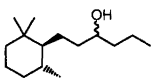
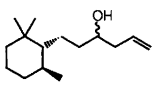
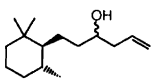
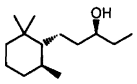
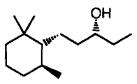
1'*R*.6'*S*-Form	Odor (threshold, ppb)	1'*R*.6'*S*-Form	Odor (threshold, ppb)
	Diffusive amber odor with slightly floral, orrisy and earthy note (400)		Faint vetiver-like woody odor (1000)
	Very diffusive sharp amber odor with slightly orrisy camphoraceous side note (56)		Faint vetiver-like woody odor slightly amber and moldy note (89)
	Very powerful diffusive sharp amber odor with slightly orris-like animal note (4)		faint vetiver-like woody odor with a little moldy side note (130)
	Powerful sweet amber odor with slightly musky note (10)		Phenolic moldy vetiver-like woody odor (300)

Table 4. Odor profiles and threshold values of a diasteromeric pair of 1-(2,2,6-trimethylcyclohexyl)alkan-3-ols.

1'*R*.6'*S*, 3*S*-Form	Odor (threshold, ppb)	1'*R*.6'*S*, 3*R*-Form	Odor (threshold, ppb)
	Powerful sharp clean amber (33)		Weak, uncharacteristic woody amber (600)

flower, fruit, etc. In perfume industries, recipes for splendid perfumes often contain a small amount of a malodorous component; for example, indole, isobutylquinoline, *n*-dodecanal, and even some mercaptan derivatives. Synthetic musk is popular as such a component.

Do our olfactory sensory systems play something like chords and discords? Excellent perfume recipes are fine art. The deception is an art, you may call it culture.

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