Chiral Metal Complexes as Discriminating Molecular Catalysts

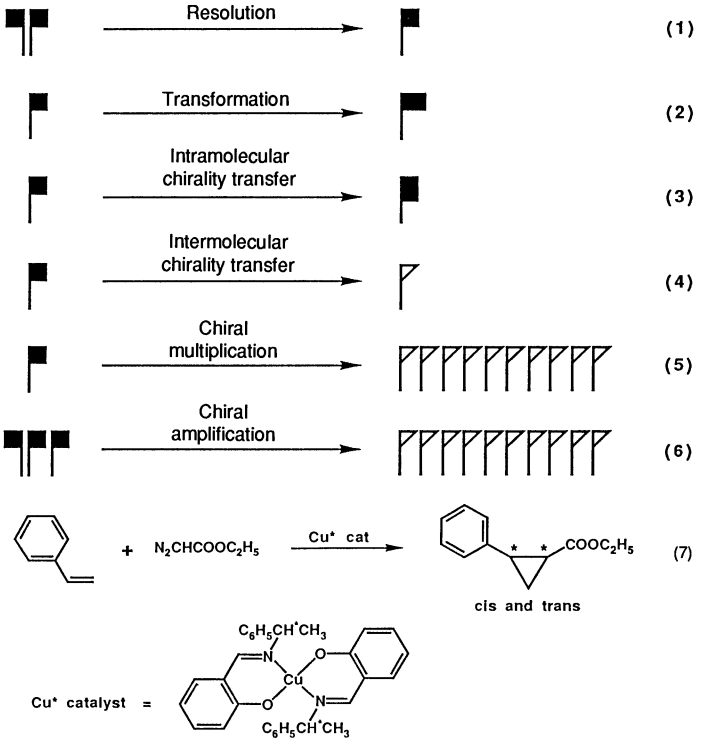
RYOJI NOYORI

As molecular recognition continues to gain importance in the biological and physical sciences as well as in the technologies of molecular electronics and optics, so has the need for efficient syntheses of chiral molecules. Chemists are fulfilling this need through use of chiral organometallic molecules. These chiral metal complexes precisely discriminate between enantiotopic atoms, groups, or faces in achiral molecules and catalyze production of a broad array of natural or unnatural substances of excellent enantiomeric purity. Because of their ability to efficiently multiply chirality, even on an industrial level, these catalysts promise to exert a general impact on molecular science and engineering.

CHIRALITY (HANDEDNESS) IS A KEY ELEMENT IN NATURE. Enzymes and other natural binding sites recognize substrates with a particular chirality to generate a variety of biological functions. Particular physical properties related to electronics and optics also occur through precise matching of molecular asymmetry. Therefore, truly efficient ways to access chiral substances constitute genuine challenges in science and technology. Synthetic chemists are meeting this challenge by developing a variety of stereoselective reactions that utilize chiral sources to prepare new asymmetric products, as shown schematically below (flags refer to right- or left-handed molecules).

Previous chirality transfer approaches, like classical optical resolution of racemates (Eq. 1) and transformation of chiral compounds (Eq. 2), have been stoichiometric in terms of chirality and require at least one equivalent of a chiral source in order to create a new chiral compound (Eqs. 3 and 4). More recently, however, certain metal complexes with chiral organic ligands have been shown to act catalytically and multiply chirality, as visualized by Eq. 5 (*1*). Compact templates with molecular weights of less than 1000 (<20 Å in length or diameter), these organometallic catalysts are neither symmetrical particles nor flat plates, but they are endowed with functionality and chirality which allow differentiation of diastereomeric transition states with accuracy of 10 kJ/mol. Such molecular catalysts not only accelerate reactions of associated substrates, but they also control the stereochemical outcome of reactions in an absolute sense.

To my knowledge, the first catalytic asymmetric reaction of prochiral compounds caused by soluble chiral metal complexes was reported in 1966 (*2*). A chiral Schiff base–Cu(II) complex was found to catalyze the enantioselective carbenoid reaction between styrene and ethyl diazoacetate to give *cis*- and *trans*-2-phenylcyclopropanecarboxylates in <10% enantiomeric excess (ee) (Eq. 7).



Such homogeneous chemistry based on the molecular architecture is obviously more rational than the heterogeneous version found 10 years earlier (*3, 4*). More recent advances have generated a number of impressive homogeneous catalysts that have greatly raised the potential of chemical synthesis. We can now produce large amounts of chiral compounds having natural and unnatural configurations with the use of only a very small quantity of a selected chiral source. This article addresses some salient aspects of this rapidly growing, important field [for reviews, see (*5, 6*)].

Catalytic Enantioselective Addition of Dialkylzincs to Aldehydes

Nucleophilic addition of organometallics to aldehydes to prepare secondary alcohols is a fundamental operation in synthetic organic chemistry. Although a catalytic process to asymmetrically add conventional organolithium or Grignard reagents to aldehydes has

The author is a professor at the Department of Chemistry, Nagoya University, Chikusa, Nagoya 464-01, Japan.

yet to be achieved, we have found that dialkylzincs (the oldest organometallic compounds, first prepared by Frankland in 1849), in the presence of catalytic amounts of certain sterically congested chiral β-dialkylamino alcohols, add to aldehydes to give secondary alcohols of high enantiomeric purity. For example, in the presence of 2% by mole of (−)-3-*exo*-(dimethylamino)isoborneol [(−)-DAIB], diethylzinc and benzaldehyde react in toluene at 0°C to give after aqueous workup (*S*)-1-phenyl-1-propanol in 98% ee and in 97% yield (*7*). This enantioselective reaction catalyzed by a soluble Zn complex has been extended to a range of alkylating agents and aldehyde substrates.

A striking nonlinear relation that has allowed for catalytic amplification of chirality (Eq. 6) is seen between the enantiomeric purity of the chiral auxiliary and that of the product from alkylation (*7–10*). When, for instance, (−)-DAIB of only 15% ee [(−)/(+) = 57.5:42.5] is used catalytically (8% by mole) in the reaction of diethylzinc and benzaldehyde, the *S* ethylation product with 95% ee is obtained. This high enantioselectivity is close to the 98% ee obtained with enantiomerically pure DAIB! The enormous departure from the anticipated linear relation in the ethylation and methylation of benzaldehyde is shown in Fig. 1. Evidently chiral and achiral catalytic systems are competing in the same reaction and, under certain conditions, turnover efficiency of the former is >600 times that of the latter. This unusual phenomenon results from strict matching of chirality through mutual enantiomer recognition (Fig. 2). The actual catalyst that induces reaction of dialkylzinc and aldehyde is a monomeric Zn complex, (2*S*)- or (2*R*)-**1**, although it normally exists as the more stable dimer **2**. Homochiral dimerization leads to (2*S*,2′*S*)-, or (2*R*,2′*R*)-2 with C_2 chirality, whereas heterochiral interaction of **1** gives a meso complex, (2*S*,2′*R*)-**2**. Reaction of equimolar amounts of dimethylzinc and enantiomerically pure (−)-DAIB affords the crystalline (1*S*,1′*S*)-**2** (R = CH_3), whereas

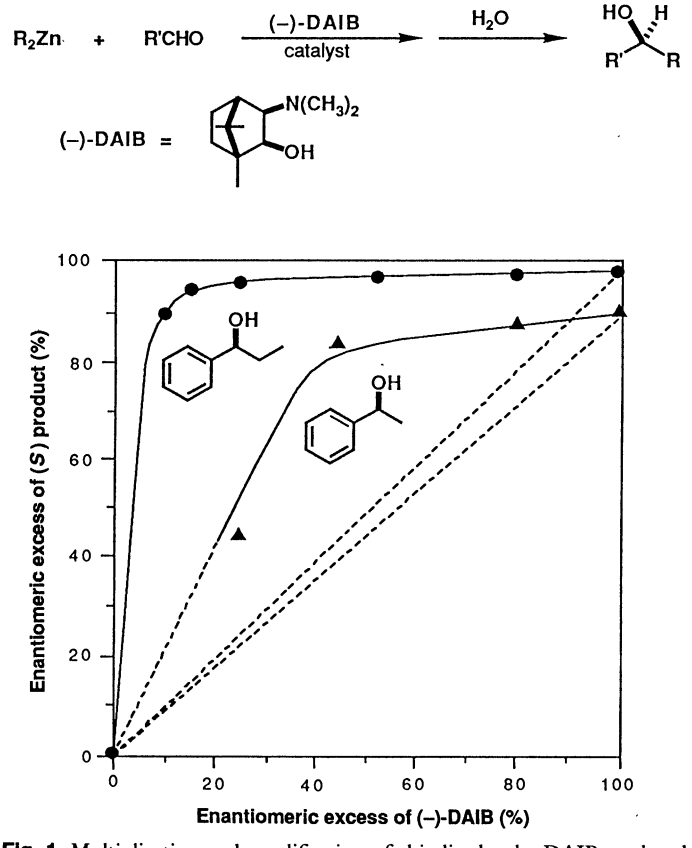


Fig. 1. Multiplication and amplification of chirality by the DAIB-catalyzed reaction of dialkylzinc and aldehydes (*9*).

reaction with racemic DAIB gives the meso isomer (2*S*,2′*R*)-**2** (R = CH_3) exclusively. Mixing enantiomeric (2*S*,2′*S*)- and (2*R*,2′*R*)-**2** in a 1:1 ratio also affords the meso complex (2*S*,2′*R*)-**2**. Thus the heterochiral interaction of enantiomers of **1** is overwhelmingly favored thermodynamically over the homochiral interaction. This result is explained by examining the x-ray crystallographic structures for the chiral and meso complexes. In the chiral complex (2*S*,2′*S*)-**2**, the central 5/4/5 tricyclic structure of syn geometry is much more congested than the meso complex's anti 5/4/5-fused ring structure. Consequently, in solution, the chiral diastereomer has greater tendency to dissociate into the reaction monomer **1** that participates in the catalytic cycle. Thus, when the partially resolved DAIB auxiliary is used, the minor enantiomer is transformed to the meso complex, while the enantiomer present in excess produces the more reactive chiral dimer. In this reaction the origin of a chirality-amplifying phenomenon has been elucidated at the molecular structure level. This example may also implicate a mechanism for the propagation of chirality in nature.

Enantioselective Catalyses by Rh(I)-BINAP Complexes

Chiral phosphine complexes of late transition metals in low oxidation states are another promising class of catalysts that promote enantioselective reactions in homogeneous phase. 2,2′-Bis-

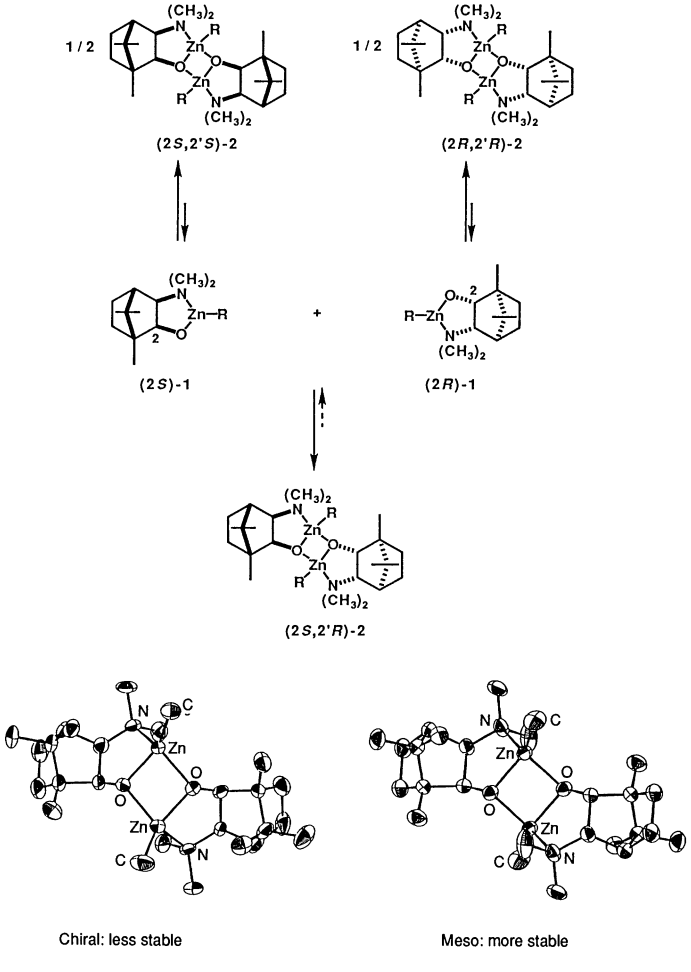


Fig. 2. Mutual recognition of enantiomeric alkylzinc alkoxides and ORTEP drawing of (2*S*,2′*S*)-**2** (R = CH_3) (left) and (2*S*,2′*R*)-**2** (R = CH_3) (right). The structures are reproduced from (*9*) by permission of the American Chemical Society.

(diarylphosphino)-1,1′-binaphthyl (BINAP), a fully arylated, C_2 symmetrical chiral diphosphine, is one of the most effective chiral ligands that have been designed (*11*). BINAP ligands can accommodate a wide variety of transition metals to form conformationally unambiguous seven-membered chelate rings containing only sp^2 carbons. The single crystal x-ray analyses of certain square planar or octahedral BINAP complexes (Ar = C_6H_5) indicate that the seven-membered rings have a highly skewed configuration that provides a chirally distinct microenvironment in which the phosphophenyl groups orient to axial and equatorial directions (Fig. 3) (*12*). These spatial characteristics exert a significant influence on the substrate coordination sites that allows for exceptional efficiency in BINAP catalysis (*13*).

Cationic Rh-BINAP complexes effect enantioselective hydrogenation of α-(acylamino)acrylic acids or esters affording protected amino acids in up to 100% ee (*11*). Even more significant is the ability of the BINAP complex to catalyze enantioselective isomerization of allylic amines to the (*E*)-enamines in >95% ee (Fig. 4) (*14*). Either antipodal enamine product is accessible through choice of the chirality of the BINAP ligand or by changing the olefin geometry. The allylic hydrogen shift is perceived to occur through a simple nitrogen-triggered mechanism without coordination of the double bond (*15*). The Rh-BINAP complex clearly discriminates between enantiotopic C-1 hydrogens of flexible allylamines through interaction with the nitrogen atoms, giving chiral enamine products through the iminium-Rh hydride intermediate.

Asymmetric Hydrogenation Catalyzed by Ru(II)-BINAP Complexes

Hydrogenation of multiple bonds to create stereo-defined tertiary carbon centers is an extremely important organic reaction. The discovery by Knowles and Horner in 1968 of the enantioselective hydrogenation of olefins (3 to 15% ee) with Rh(I) complexes that have chiral unidentate phosphines (*16*) was followed by seminal contributions of, among others, Kagan, Knowles, Bosnich, Kumada, Brunner, Ojima, Achiwa, and Nagel, who refined the structure of the bidentate phosphine ligand. Optical yields of >90% are now obtainable in hydrogenation of a series of α-(acylamino)acrylic acids (*17*) and a detailed reaction mechanism has been elucidated by

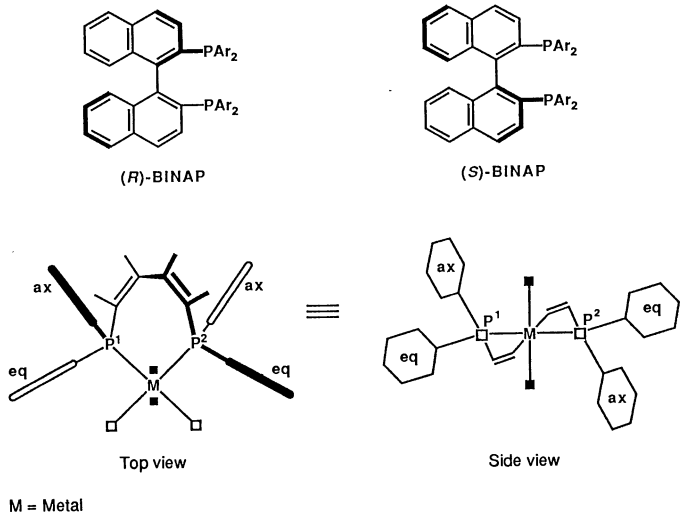


Fig. 3. The ligand BINAP and the schematic representation of δ-configurated (*S*)-BINAP metal complexes (Ar = C_6H_5; 1,1′-binaphthyl skeleton omitted for clarity).

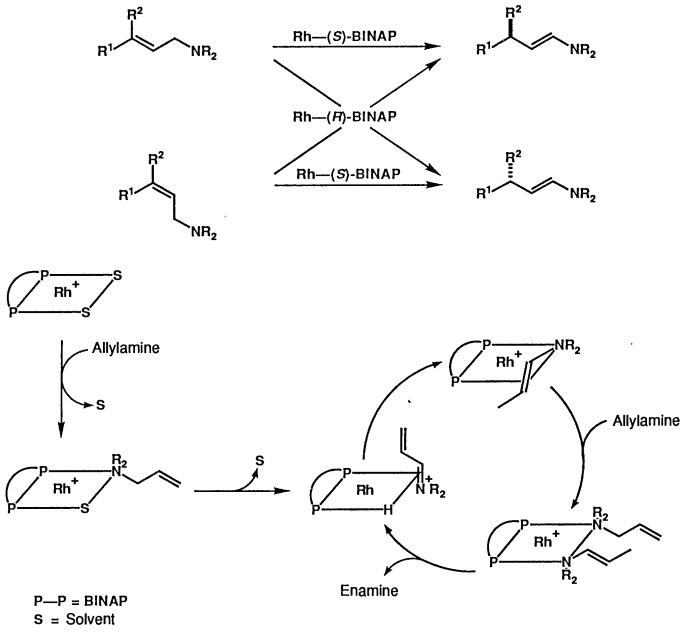
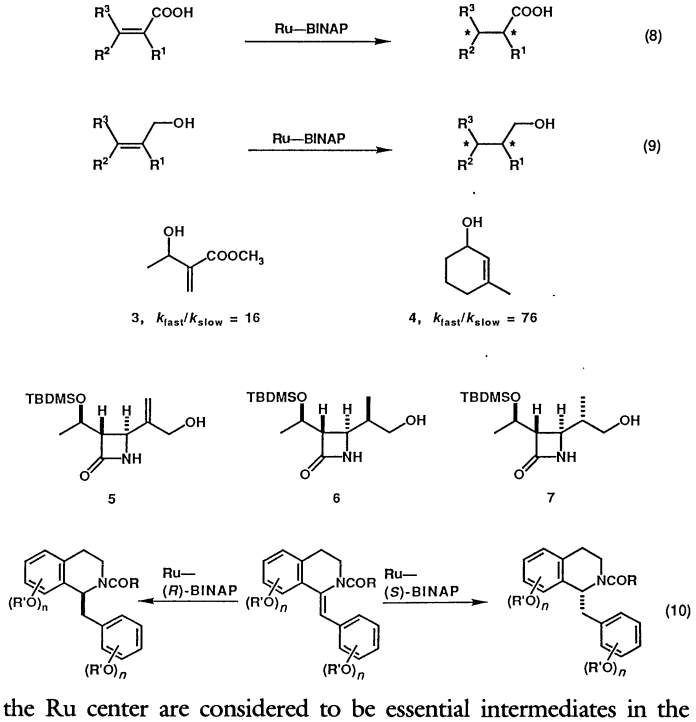


Fig. 4. Enantioselective 1,3-hydrogen shift in allylic amines.

Halpern and Brown (*18*). Unfortunately, the scope of the Rh-catalyzed reaction is limited.

In contrast, Ru-BINAP–catalyzed hydrogenation finds spectacular generality (*13, 19*). Ruthenium(II) dicarboxylate complexes of the type Ru(OCOR)$_2$(BINAP) catalyze hydrogenation of prochiral α,β- and β,γ-unsaturated carboxylic acids (*20*) as well as allylic and homoallylic alcohols (*21*) to give the corresponding optically active saturated compounds (Eqs. 8 and 9). Chelate complexes in which the olefinic bond and carboxylate or hydroxyl group interact with



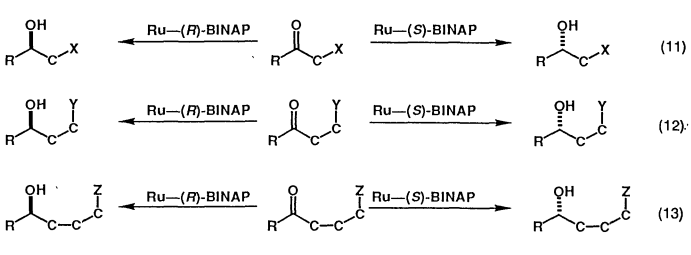
the Ru center are considered to be essential intermediates in the hydrogenation mechanism, which is thought to proceed through a Ru monohydride species. In contrast, the Rh-promoted reaction occurs through a metal dihydride intermediate. The sense and extent of asymmetric induction of the Ru-BINAP–catalyzed reaction are

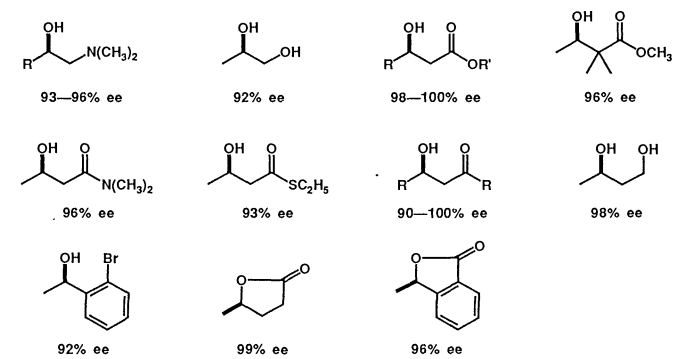
highly dependent on both the substrate substitution pattern and hydrogen pressure. Under optimized conditions, an ee as high as 90 to 99% can be obtained.

Enantiomers of some secondary allylic alcohols such as **3** or **4** are hydrogenated at different rates, allowing for a kinetic resolution of enantiomers (*22*). The Ru–(*S*)-BINAP–catalyzed hydrogenation of enantiomerically pure allylic alcohol **5** [TBDMS = *tert*-$C_4H_9(CH_3)_2Si$] affords a 99.9:0.1 mixture of 1β-methyl compound **6** (an important intermediate for 1β-methylcarbapenem synthesis) and 1α stereoisomer **7** (*23*). Since use of the (*R*)-BINAP catalyst gives only moderate diastereoselectivity (**6**/**7** = 22:78), the extremely high selectivity found above results from the cooperation of intramolecular asymmetric induction (β/α = 17:1) and efficient catalyst-to-olefin chirality transfer (*R**/*S** = 59:1). Thus, combination of the principles of Eqs. 3 and 5 (*24*) provides an impressive enhancement of diastereoselectivity.

Another useful reaction is the enantioselective hydrogenation of *N*-acyl-(*Z*)-1-alkylidene-1,2,3,4-tetrahydroisoquinolines to give either 1*R* or 1*S* products in 95 to 100% ee (Eq. 10). By this process a general asymmetric synthesis of isoquinoline alkaloids has been realized (*25*).

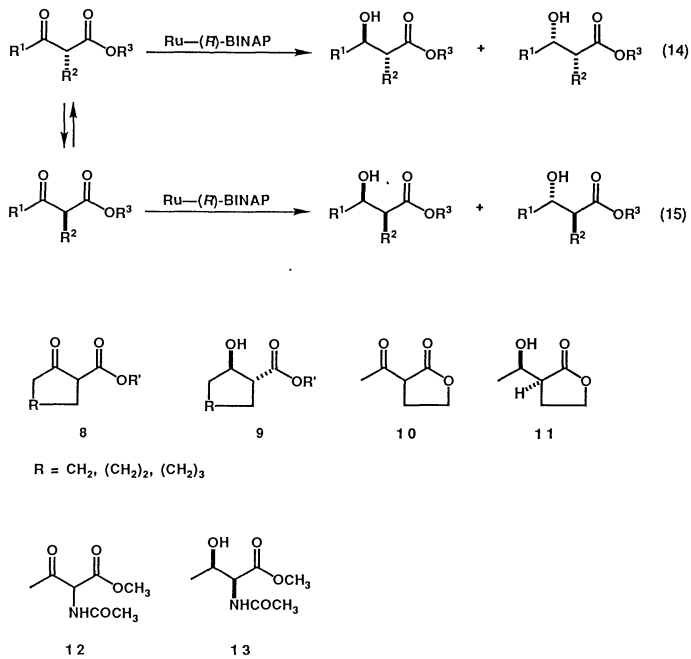
Although asymmetric hydrogenation of ketones is another difficult problem in chemical synthesis, a wide variety of functionalized ketones are now convertible to their respective optically active secondary alcohols through homogeneous hydrogenation with halogen-containing Ru-BINAP catalysts in alcoholic media, as generalized in Eqs. 11 through 13 (*26*). The reaction proceeds in a highly enantioselective and predictable fashion. Some chiral products obtained from (*R*)-BINAP catalysis are shown above. A general mechanism to describe this selective process involves initial coordination of the carbonyl oxygen and an adjacent heteroatom (such as nitrogen, oxygen, or halogen) to create a five- to seven-membered, metal-chelated ring complex prior to hydrogen transfer.





Double stereodifferentiation (Eq. 3 and Eq. 5) increases the degree of stereoselection when 2,4-pentanedione, a symmetrical prochiral β-diketone, is subjected to hydrogenation with the (*R*)-BINAP complex. The reaction proceeds through the *R* hydroxy ketone intermediate in 98.5% to give ultimately almost enantiomerically pure (*R,R*)-2,4-pentanediol and the meso diol in a 99:1 ratio.

In classical resolution or conventional kinetic resolution (Eq. 1), the yield of one enantiomer does not exceed 50% (*27*). In contrast, the Ru-BINAP–catalyzed hydrogenation of certain optically labile α-substituted β-keto esters proceeds with dynamic resolution to afford one of the four possible stereoisomeric hydroxy esters in >90% yield as outlined in Eqs. 14 and 15 (*28*). In order to achieve such an ideal second-order asymmetric catalysis, three conditions



must be satisfied: (i) racemization of the keto ester substrate is sufficiently faster than hydrogenation; (ii) facial discrimination by the chiral catalyst is excellent; and (iii) the structure or functional group of the substrate allows for a clear distinction between the stabilities of syn and anti transition states in the stereo-determining step. Racemic cyclic ketones of type **8** are, for example, hydrogenated with [$RuCl(C_6H_6)$ (*R*)-BINAP]Cl in dichloromethane to give the *R* alcohols **9** with high anti selectivity in 90 to 95% ee and in 90% yield. On the other hand, hydrogenation of racemic lactonic ketone **10** with the same catalyst produces *R* alcohol **11** in 94% ee with a 98:2 syn selectivity. Hydrogenation of certain acyclic keto esters possessing amide groups also proceeds with high syn selectivity. For instance, racemic **12** is converted to protected threonine (**13**) in 98% ee.

Opportunities

The efficiency of chiral organometallic catalysts rivals that of natural enzymes. This chemical means is clean, operationally simple, economical, and capable of being conducted on a large scale with a sufficiently high substrate-to-catalyst ratio and high substrate concentration (up to 50%) in organic solvents. It is of industrial significance, particularly in the fields of pharmaceuticals, agrochemicals, flavors, and fragrances (Fig. 5) (*29*). The degree of enantioselection in the Cu-carbenoid reaction (Eq. 7) (*2, 30*) was at first not practically meaningful; however, through extensive systematic screening of Cu–Schiff base catalysts a dramatic improvement of the optical yield has been achieved, and now (*S*)-2,2-dimethylcyclopropanecarboxylic acid (*31*), a component of cilastatin, which is an excellent in vivo stabilizer of antibiotic imipenem, is commercially synthesized by this catalytic process (Sumitomo Chemical Industry, Japan, and Merck Sharp & Dohme Co.). The Rh-catalyzed enantio-

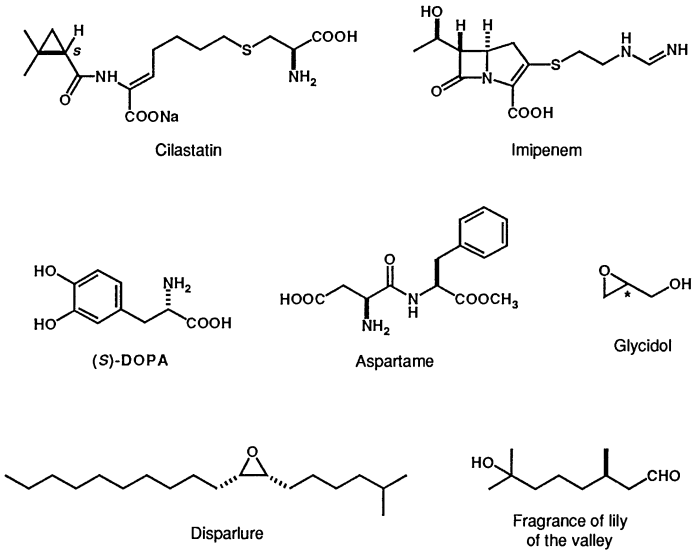


Fig. 5. Commercial applications of metal-complex–catalyzed asymmetric reactions.

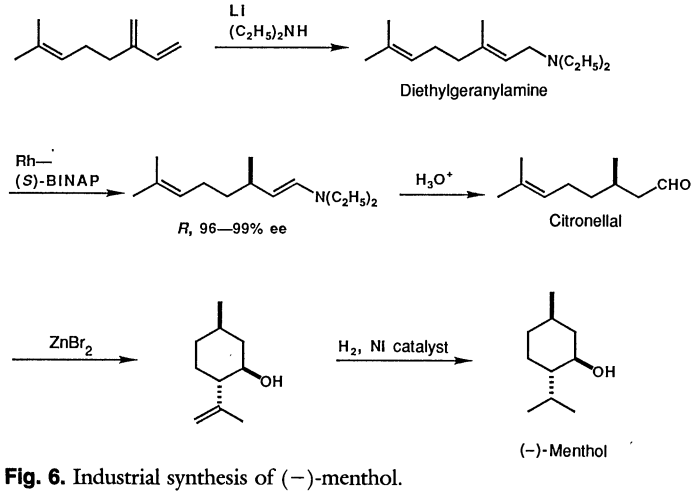


Fig. 6. Industrial synthesis of (−)-menthol.

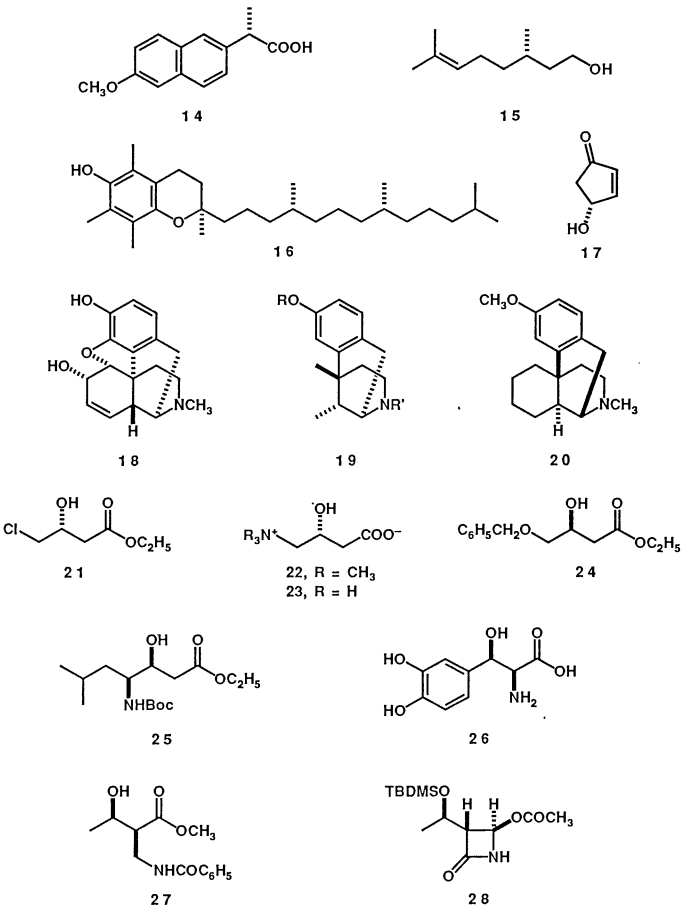


Fig. 7. Possible applications of the Ru-BINAP–catalyzed hydrogenation.

selective hydrogenation has been used to commercially produce (*S*)-DOPA, which is used to treat Parkinson's disease (Monsanto Co. and VEB Isis-Chemie, DDR) (*32*). (*S*)-Phenylalanine, a component of the nonnutritive sweetner aspartame is also prepared by Rh-catalyzed hydrogenation (Anic S.p.A., Italy). The Sharpless epoxidation of allylic alcohols with chiral Ti(IV)-tartrate complexes (*33*) has led to economical syntheses of glycidol (Arco Co.), a useful chiral building block, as well as disparlure (J. T. Baker Co. and Shanghai Institute for Organic Chemistry), a gypsy moth pheromone. At present, the world's largest industrial application of asymmetric catalysis features Rh-BINAP–promoted isomerization of diethylgeranylamine to (*E*)-(*R*)-citronellal enamine in 96 to 99% ee on a 7-ton scale (Figs. 4 and 6). Enantiomeric purity of naturally occurring (*R*)-citronellal rarely exceeds 80%. This enantioselective catalysis now allows production of (−)-menthol and other terpenic substances such as the fragrance from the lily of the valley flower totaling ~1500 tons per year (Takasago International Co., Japan).

Some new Ru-BINAP–catalyzed hydrogenation processes should soon be industrialized after technical refinements. Certain viable possibilities are given in Fig. 7 (*13, 19*). The hydrogenation of α-(6-methoxy-2-naphthyl)acrylic acid gives the antiinflammatory agent naproxen (**14**) in 97% ee. Hydrogenation of geraniol and nerol, affording natural and unnatural citronellol in >96% ee, proceeds without saturation of the C6-C7 double bond with a substrate-to-catalyst mole ratio as high as 50,000. Notably, the enantiomeric purity of synthetic (*S*)-citronellol (**15**) is superior to that of the precious natural product obtained from rose oil, which is at most 92% ee. A combination of both Ru- and Rh-BINAP chemistry (asymmetric hydrogenation and allylamine isomerization) may be applicable to synthesis of the side chain of α-tochopherol (vitamin E, **16**). The kinetic resolution of allylic alcohols by Ru-catalyzed hydrogenation provides a practical way to chiral cyclopentenone **17**, an important building block for the three-component synthesis of prostaglandins (*34*). A general isoquinoline synthesis through enamide hydrogenation (Eq. 10) followed by Grewe-type cyclization allows concise preparation of morphine (**18**), benzomorphans (**19**), and morphinans including the bronchodilating agent dextromethorphan (**20**) (*35*). Significantly, a range of structurally flexible β-keto esters are hydrogenated to optically active β-hydroxy esters in nearly 100% yield with up to 100% ee. Chloro compound **21** thus obtained is a useful intermediate for the synthesis of carnitine (**22**), responsible for transport of long-chain fatty acids through membranes, and GABOB (**23**), an anti-epilepic and hypotensive drug (*36*). Benzyloxy product **24** is a building block for synthesis of compactin, a human menopausal gonadotropin–coenzyme A reductase inhibitor. A protected statine (**25**, Boc = benzyloxycarbonyl) with 3*S*,4*S* threo configuration is accessible from the corresponding chiral β-keto ester through double asymmetric induction (*37*). This is currently the best method for synthesizing this unusual amino acid and its analog that may be useful for preparing pepstatin and related aspartic proteinase inhibitors. The dynamic kinetic resolution illus-

trated in Eqs. 14 and 15 is useful for synthesis of L-DOPS (**26**), an anti-Parkinsonian agent, as well as the 2,3-syn hydroxy ester **27** which is convertible to **28**, a key intermediate for synthesis of antibiotic carbapenems (*28*). Obviously, the scope of the Ru-BINAP–catalyzed hydrogenation is enormous.

Outlook

In contrast to the single-handed, lock-and-key specificity of enzymatic processes, chemical synthesis with chiral organometallic catalysts is characterized by its generality. In principle, any chiral structures can be generated through rational modification of the catalyst's molecular structure. Since organic reactions responsible for carbon-carbon bond formation, oxidation, reduction, and functional group transformation make use of metallic species extensively, the chiral metal-complex strategy is generally valid and broadly powerful. This chemical methodology has only begun to contribute to industrial production and molecular sciences where chirality plays a significant role. This article is not comprehensive and the above-mentioned examples are only a sample of this rapidly progressing science. High degrees of stereoselection have already been seen in various catalytic organometallic reactions such as hydrosilylation (*38*), hydroboration (*39*), vicinal hydroxylation of olefins (*40*), allylic alkylation (*41*), organometallic–organic halide coupling (*42*), olefin hydroformylation (*43*), aldol-type reactions (*44*), olefin hydrovinylation (*45*), and propylene polymerization (*46*). Further, certain chiral metal complexes acting as Lewis acids promote many other kinds of enantioselective organic reactions (*47*), such as the Diels-Alder reaction (*48*) and ene reaction (*49*).

The concern of synthetic chemists to create stereo-defined structures has relied heavily on manipulation of spatial factors, but this is insufficient. Asymmetric catalysis is a four-dimensional chemistry, and high efficiency is only accessible through a combination of both an ideal three-dimensional structure (x, y, z) and appropriate kinetics (t). As our understanding of metallo-organic chemistry increases, new stereoselective catalytic reactions are certain to be developed (*50*).

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