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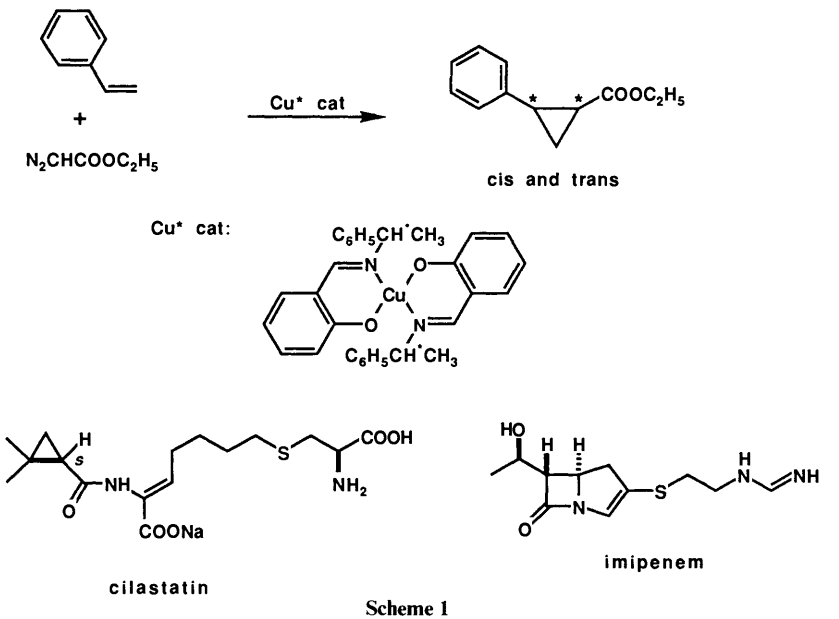
CENTENARY LECTURE
Chemical Multiplication of Chirality: Science and Applications

By R. Noyori
DEPARTMENT OF CHEMISTRY, NAGOYA UNIVERSITY, CHIKUSA, NAGOYA 464-01, JAPAN

1 Introduction

Chirality plays a central role in science and technology. A wide range of significant physical, chemical, and biological functions are generated through precise molecular recognition which requires strict matching of chirality. For a long time access to highly enantiomerically pure compounds, at least in a practical sense, was thought to be Nature's monopoly and has indeed been accomplished by biological or biochemical transformations. Efficient creation of optically active organic molecules from prochiral compounds by chemical means, though it is challenging, has remained difficult, and only optical resolution and structural modification of naturally occurring chiral substances have provided complements in this respect. However, assiduous efforts made by synthetic organic chemists in the last two decades are converting the chemists' dream into reality. In order to maximize synthetic efficiency, 'multiplication of chirality', namely, stereoselective production of a large quantity of a chiral target compound utilizing a catalytic amount of chiral source, is obviously desirable. Enantioselective catalysis using chiral metal complexes, among various possibilities, provides one of the most general, flexible methods for this purpose.[1] Metallic elements possess a variety of catalytic activities, and permutation of organic ligands or auxiliaries directing the steric course of the reaction is practically unlimited. Accordingly, in principle, one can generate any dynamic properties at will through molecular architecture using accumulated chemical knowledge. To this end, creation of a single, highly reactive catalyic species possessing excellent chiral recognition ability is required. Besides the choice of central metals therefore, molecular design of the chiral modifiers is a particularly significant task. The efficient ligands must be endowed with a suitable functionality; an appropriate element of symmetry; substituents capable of differentiating space either sterically or electronically; skeletal rigidity or flexibility (depending on the nature of the reaction), *etc.*—all of which contribute to accomplish highly enantioselective catalyses.[2]

[1] For the present state of this subject, see R. Noyori and M. Kitamura, in 'Modern Synthetic Methods 1989', ed. R. Scheffold, Springer Verlag, Berlin, p. 115.
[2] R. Noyori and H. Takaya, *Chem. Scr.*, 1985, **25**, 83.



Scheme 1

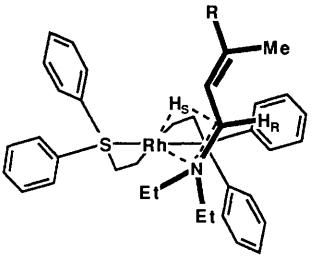
2 Discovery and Opportunities

To our best knowledge, the first example of asymmetric synthesis from prochiral compounds *catalysed* by homogeneous chiral metal complexes appeared in the literature in 1966.[3] A chiral Schiff base–Cu^{II} complex was found to catalyse decomposition of ethyl diazoacetate in styrene to give *cis*- and *trans*-2-phenylcyclopropanecarboxylates in $<10\%$ e.e., proving the existence of a reactive Cu carbenoid placed in a chiral environment. The intermediary carbenoid was also trapped by racemic 2-phenyloxetane leading to optically active furan derivatives. Later extensive, systematic screening of the chiral Schiff bases resulted in a dramatic improvement of the optical yield of the cyclopropanation, allowing asymmetric synthesis of chrysanthemic acid derivatives in up to 94% e.e.[4] This chemistry has been successfully applied to industrial synthesis of (*S*)-2,2-dimethylcyclopropanecarboxylic acid, a component of cilastatin which serves as an excellent inhibitor of dehydropeptidase-I increasing *in vivo* stability of antibiotic imipenem (Sumitomo Chemical Co., Japan, and Merck Sharp & Dohme Co., USA) (Scheme 1).

Among other asymmetric catalyses working in industry at this moment, perhaps the largest is a process involved in the synthesis of (−)-menthol

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

[4] T. Aratani, *Pure Appl. Chem.*, 1985, **57**, 1839.



R = $(CH_3)_2C{=}CHCH_2CH_2$

(1)

(Takasaga International Co., Japan). The key step is the Rh–BINAP[5] catalysed enantioselective isomerization of diethylgeranylamine to citronellal diethylenamine proceeding in 96—99% optical yield.[6] The optical purity of the synthetic citronellol is much higher than that of the natural product; *ca.* 80%. The technical refinement has led to an innovative catalytic process working on up to a 7 ton scale. Here, use of atropisomeric BINAP ligand has played a key role in the successful asymmetric catalysis. The fully aromatic diphosphine having an axial element of chirality was first prepared by optical resolution of the racemate through an optically active amine–Pd^{II} complex,[5a,b] but is now obtainable more conveniently by resolution of its dioxide, BINAPO, with camphorsulphonic acid or *O*-dibenzoyltartaric acid followed by reduction with trichlorosilane.[7] A number of BINAP analogues can be prepared in such a way (Scheme 2).

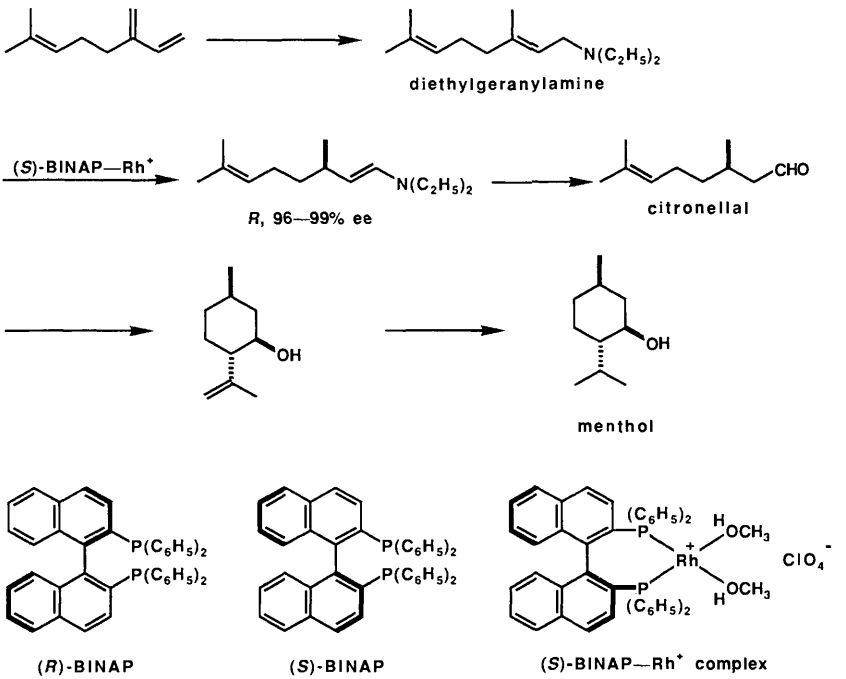
Olefinic double bonds are known to shift *via* a metal hydride addition–elimination mechanism or a π-allylmetal hydride pathway. However, the allylamine to enamine isomerization was revealed to occur *via* a new, nitrogen-triggered mechanism (Scheme 3).[8] The nitrogen-coordinated allylamine–Rh^+ complex causes four-centred hydride elimination from C(1) to generate a transient iminium–RhH complex. Delivery of the hydrogen from Rh to C(3) gives the enamine η^2- and then η^3-complexes. The latter, having an aza-allyl structure, serves as the chain carrier in the catalytic cycle. The overall 1,3-hydrogen shift in the geranylamine occurs in a suprafacial manner from its *s-trans*-type conformer, as proved by the deuterium labelling experiments. The cationic Rh–BINAP complexes differentiate efficiently between pro-*R* and pro-*S* hydrogens at C(1) through interaction with the adjacent nitrogen atom (Scheme 4). A transition-

[5] (*a*) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, and R. Noyori, *J. Am. Chem. Soc.*, 1980, **102**, 7932; (*b*) A. Miyashita, H. Takaya, T. Souchi, and R. Noyori, *Tetrahedron*, 1984, **40**, 1245; (*c*) K. Toriumi, T. Ito, H. Takaya, T. Souchi, and R. Noyori, *Acta Crystallogr., Sect. B*, 1982, **38**, 807; (*d*) S. Inoue, M. Osada, K. Koyano, H. Takaya, and R. Noyori, *Chem. Lett.*, 1985, 1007.

[6] (*a*) K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, and 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, and S. Otsuka, *J. Am. Chem. Soc.*, 1984, **106**, 5208.

[7] (*a*) H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, and R. Noyori, *J. Org. Chem.*, 1986, **51**, 629; (*b*) H. Takaya, S. Akutagawa, and R. Noyori, *Org. Synth.*, 1988, **67**, 20.

[8] H. Takaya, K. Tani, S. Otsuka, S. Inoue, T. Sato, and R. Noyori, to be published.



Scheme 2

state model in the Rh–(*S*)-BINAP catalysed reaction is illustrated by structure (1) (naphthalene rings are omitted for clarity).

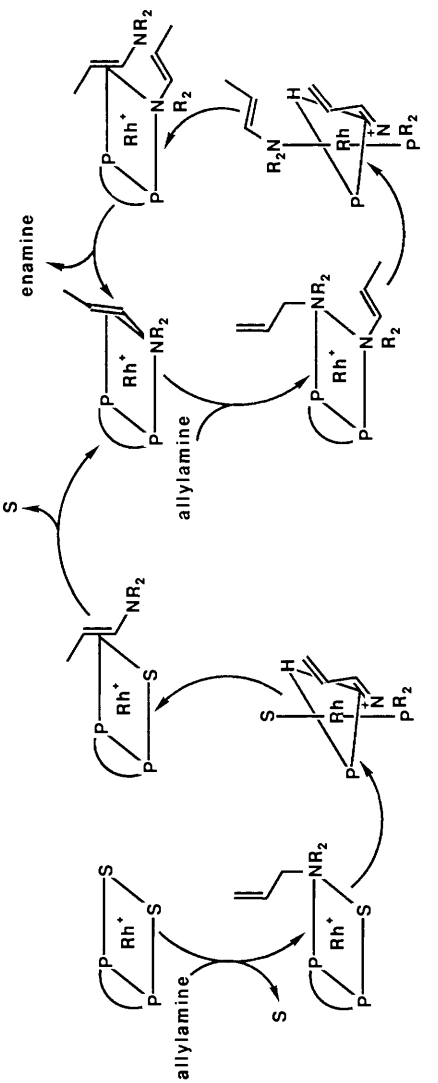
In principle, any donor groups including olefinic bond, heteroatom bases, carbanions, heteroanions, etc. are able to activate their adjacent C–H bonds through coordination to appropriate unsaturated transition metal centres. The resulting metal hydride complexes, depending on the situations, undergo unique chemical transformations. When racemic 4-hydroxy-2-cyclopentenone was exposed to 0.5 mol% of a cationic Rh–(*R*)-BINAP complex[5] in THF at 0 °C, double bond isomerization occurred with 5:1 enantiomer discrimination to afford unreacted (*R*)-hydroxy enone in 91% e.e. in 27% yield and 1,3-cyclopentanedione in 61% yield (Scheme 5).[9]

3 Ruthenium-catalysed Asymmetric Hydrogenation

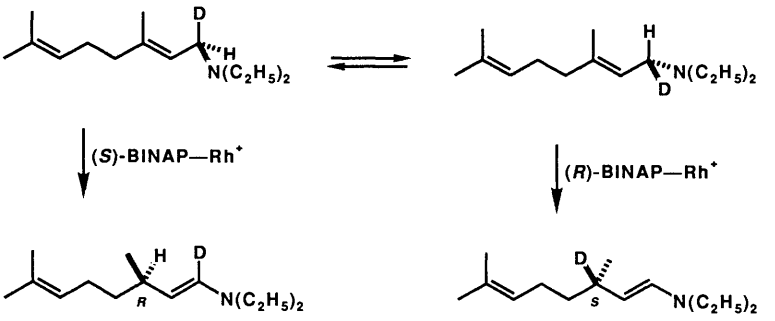
Homogeneous asymmetric hydrogenation, discovered in 1968,[10] has been one of the most exciting subjects in organic chemistry in the last two decades and a

[9] M. Kitamura, K. Manabe, R. Noyori, and H. Takaya. *Tetrahedron Lett.*, 1987, **28**, 4719.

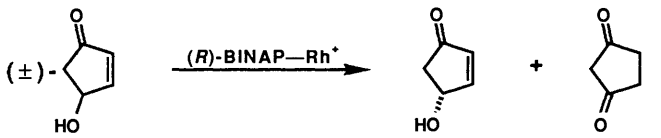
[10] (*a*) L. Horner, H. Siegel, and H. Büthe, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 942; (*b*) W. S. Knowles and M. Sabacky, *J. Chem. Soc., Chem. Commun.*, 1968, 1445.



Scheme 3



Scheme 4

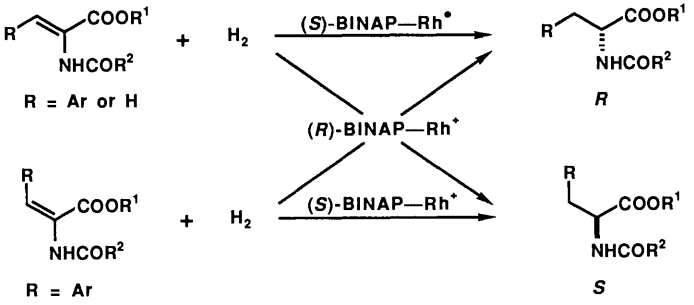


Scheme 5

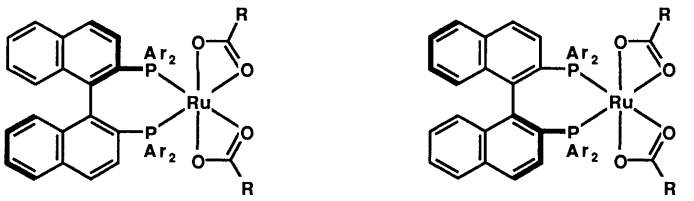
number of impressive chemistries have been presented.[11] In addition, the catalysis is of practical significance. (*S*)-DOPA, a drug for the treatment of Parkinson's disease, has been prepared at Monsanto Co., USA,[12] and VEB Isis-Chemie, DDR, by using hydrogenation of a (*Z*)-(α-acetamido)cinnamic ester with soluble Rh complex catalysts possessing a chiral phosphine or phosphinite ligand. The same method was used for commercial production of (*S*)-phenylalanine, a component of the non-nutritive sweetener Aspartame (Anic S.p.A., Italy).[13] Thus a variety of natural and unnatural amino acids are now available in >90% e.e. by enantioselective hydrogenation but, unfortunately, the scope of the Rh-catalysed reaction is not very wide. For example, $[Rh(binap)(CH_3OH)_2]ClO_4$ caused hydrogenation of dehydroamino acid derivatives (Scheme 6) with nearly perfect enantioselectivities,[5a,b] whereas optical yields of the reactions of geraniol or nerol with varying conditions did not exceed 70%.[5d] In view of the general importance of hydrogenation in organic synthesis, we have been intrigued by the possibility of developing a catalyst system capable of adopting a wide range of olefinic substrates. In this context, recent invention of Ru–BINAP dicarboxylate complexes[14] extended the utility of asymmetric hydrogenation to a great extent (Figure 1).

The Ru dicarboxylate complexes undergo ligand exchange reaction with α,β- or β,γ-unsaturated carboxylic acids, resulting in highly enantioselective (80—100%) hydrogenation.[15] Thus, with many substrates, the highest enantioselectivities

[11] Pertinent reviews: (*a*) J. Halpern, in 'Asymmetric Synthesis', Vol. 5, ed. J. D. Morrison, Academic Press, New York, 1985, Chapter 2; (*b*) K. E. Koenig, *ibid.*, Chapter 3.
[12] W. S. Knowles, *J. Chem. Educ.*, 1986, **63**, 222.
[13] H. B. Kagan, *Bull. Chem. Soc. Fr.*, 1988, 846.
[14] T. Ohta, H. Takaya, and R. Noyori, *Inorg. Chem.*, 1988, **27**, 566.
[15] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, and R. Noyori, *J. Org. Chem.*, 1987, **52**, 3174.



Scheme 6



Δ-(*R*)-BINAP—Ru dicarboxylate

Λ-(*S*)-BINAP—Ru dicarboxylate

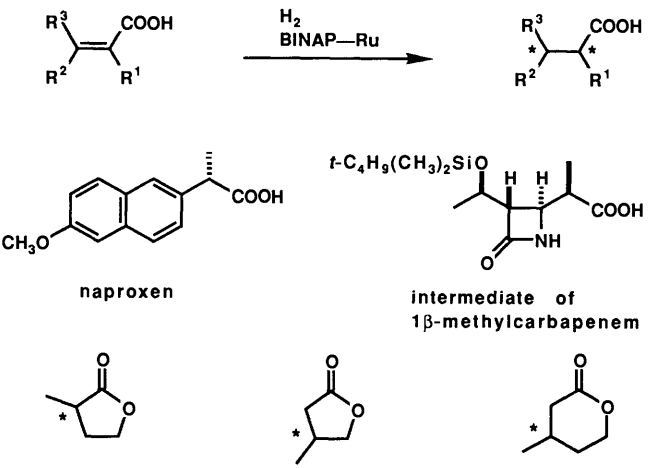
Figure 1

have been recorded. Methyl esters are inert to the hydrogenation. Alcohols are the solvents of choice. The sense and extent of the asymmetric induction are highly dependent on the substitution pattern of the substrates and reaction conditions, particularly the hydrogen pressure. Anti-inflammatory (*S*)-naproxen was prepared in 97% e.e. under a high-pressure condition. This method is also applicable to synthesis of a 1β-methylcarbapenem precursor and some optically active methylated γ- and δ-lactones (Scheme 7).

Olefins containing certain neutral donor functionalities are also hydrogenated in a satisfactory manner.[16] The Ru–BINAP catalysed hydrogenation of *N*-acyl-(*Z*)-1-benzylidene-1,2,3,4-tetrahydroisoquinolines in a mixture of ethanol and dichloromethane leads consistently to (1*R*)- or (1*S*)-benzyltetrahydroisoquinolines in nearly quantitative yield and in 95—100% e.e.[17] With Rh complexes such as [Rh(binap)(cod)]ClO_4 or [Rh(binap)$(CH_3OH)_2$]ClO_4, the hydrogenation proceeded in lower optical yield (*ca.* 75%) and with opposite enantioselection. The asymmetric hydrogenation followed by removal or modification of the *N*-acyl groups gave tetrahydropapaverine, laudanosine, norreticuline (biogenetic precursor of morphine), tretoquinol (bronchodilating agent), *etc.*

[16] For a review on stereoselective olefin hydrogenation directed by functional groups, see J. M. Brown, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 190.

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



Scheme 7

which became homochiral by single recrystallization. The reaction of the simple 1-methylene substrate affords, after deacylation, salsolidine in 96% e.e. This procedure is applicable to the synthesis of natural morphine, various benzomorphan analogues such as metazocine and pentazocine, morphinans including dextromethorphan (anticough agent), *etc.* (Figure 2).[18] This discovery has thus realized a general asymmetric synthesis of isoquinoline alkaloids.[19]

The Ru-catalysed hydrogenation of prochiral allylic alcohols exhibits unprecendented efficacy. Thus geraniol and nerol are hydrogenated in methanol containing a Ru–BINAP dicarboxylate complex to give (*S*)- or (*R*)-citronellol in 96—99% e.e.[20] Initial hydrogen pressure higher than 30 atm gave satisfactory results. Either natural or unnatural forms can be made flexibly by changing the chirality of the catalyst or geometry of the olefinic substrates. The enantiomeric purity of the synthetic citronellol exceeds the highest value of the natural product, 92%. The substrate/catalyst mole ratio is extremely high and, in certain cases, the efficiency of the chiral multiplication, defined as [major enantiomer − minor enantiomer] (in mole)/chiral source (in mole), approaches 48,500! Notably, in this hydrogenation, only allylic C(2)–C(3) double bonds are saturated and nonallylic C(6)–C(7) double bonds remain intact. Homogeraniol was hydrogenated in 92% optical yield with the same enantioselection but the bis-homologue was inert to the standard reaction conditions. This hydrogenation is usable for the stereoselective synthesis of side chains of vitamin E and K_1 (Scheme 8).

[18] M. Kitamura, Y. Hsiao, R. Noyori, and H. Takaya, *Tetrahedron Lett.*, 1987, **28**, 4829.
[19] For synthesis *via* stoicheiometric enantioselective alkylation, see A. I. Meyers, *Aldrichimica Acta*, 1985, **18**, 59.
[20] H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, and R. Noyori, *J. Am. Chem. Soc.*, 1987, **109**, 1596, 4129.

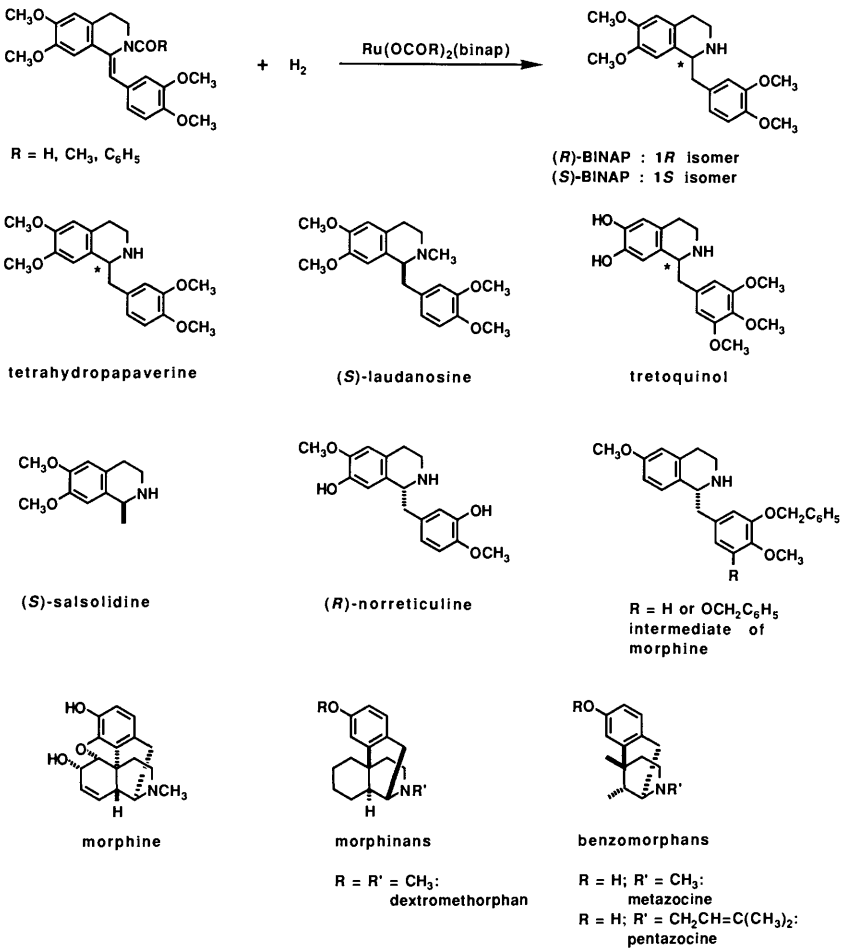
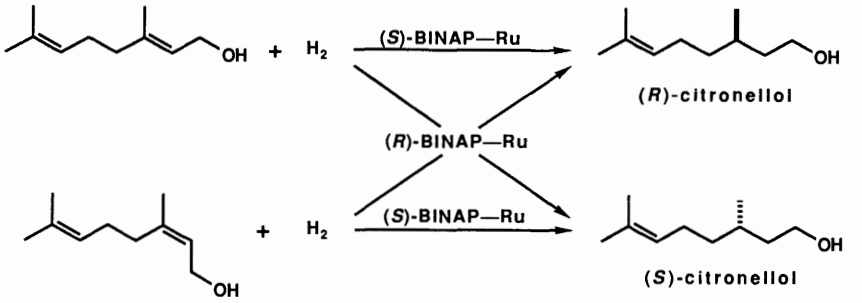
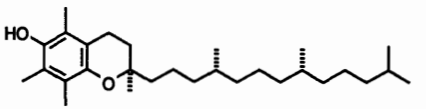


Figure 2

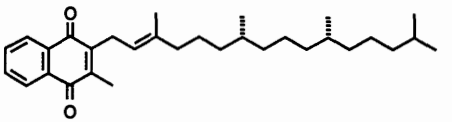
Chiral allylic secondary alcohols can be resolved efficiently by homogeneous hydrogenation catalysed by the Ru–BINAP diacetate complexes.[21] The combined effects of intramolecular and intermolecular asymmetric induction give up to 76:1 differentiation between the enantiomeric cyclic unsaturated alcohols. For instance, when racemic 3-methyl-2-cyclohexenol (Figure 3) was hydrogenated with the Ru–(*R*)-BINAP complex in methanol, at 46% conversion, *R*,*R*-configurated *trans*-3-methylcyclohexenol was obtained in 95% e.e. At 54% conversion, the slow-reacting *S*

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





vitamin E



vitamin K_1

Scheme 8

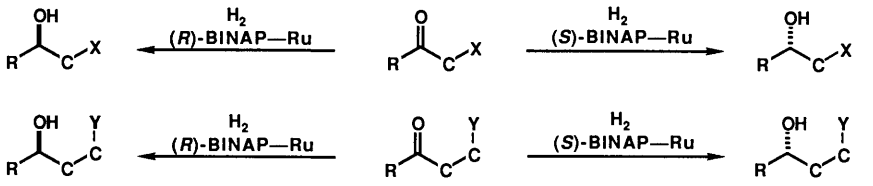
k_{fast}/k_{slow} = 76 k_{fast}/k_{slow} = 11

Figure 3

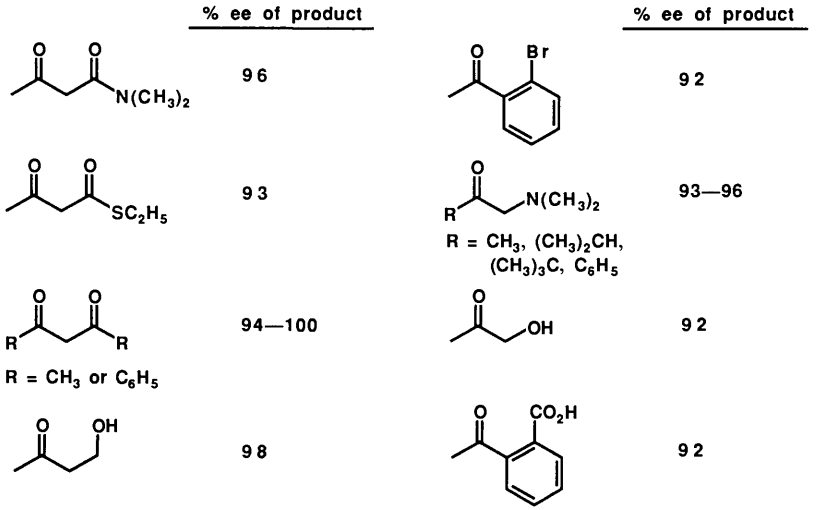
enantiomer was recovered in >99% e.e. A significant application includes a practical resolution of 4-hydroxy-2-cyclopentenone (Figure 3), an important building block for the three-component coupling prostaglandin synthesis.[22]

Homogeneous asymmetric hydrogenation of ketones has remained far less fruitful than the catalysis of olefinic substrates. Now, however, a variety of functionalized ketones can be hydrogenated with synthetically useful enantioselectivities and in a predictable manner with the aid of RuX_2(binap) [empirical formula; X = Cl, Br, I; prepared by mixing $Ru(OCOCH_3)_2$(binap) and HX in a

[22] (*a*) R. Noyori and M. Suzuki, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 847; (*b*) M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 4718; (*c*) Y. Motita. M. Suzuki, and R. Noyori, *J. Org. Chem.*, 1989, **54**, 1785.



X, Y = heteroatom
C = sp^2 or nonstereogenic sp^3 carbon



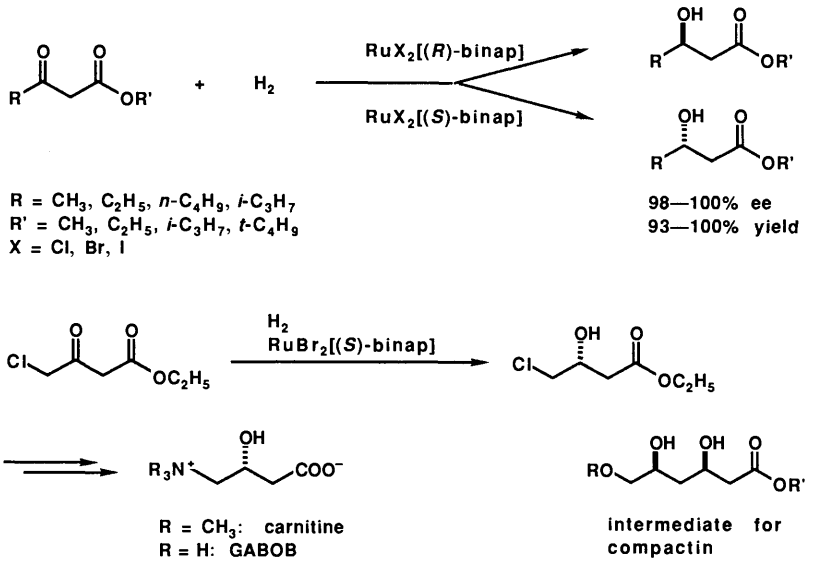
Scheme 9

1:1 mole ratio][23,24] or $Ru_2Cl_4(binap)_2(C_2H_5)_3N$.[25] The general sense of the asymmetric induction indicates that the key factor in the enantioface differentiation is the simultaneous coordination of the carbonyl oxygen and heteroatom, X or Y, to the Ru atom forming a five- and six-membered chelate ring, respectively. Some nitrogen- and oxygen-containing directive groups include dialkylamino, hydroxyl, siloxyl, keto, alkoxycarbonyl, alkylthiocarbonyl, dialkylaminocarbonyl, carboxyl, *etc.*[22] To our surprise, halogen atoms were revealed to facilitate the carbonyl hydrogenation and to direct the stereochemical outcome. Thus *o*-bromoacetophenone gave the corresponding alcohol in 92% e.e. and 97%

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

[24] M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 629.

[25] T. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa, and S. Akutagawa, *J. Chem. Soc., Chem. Commun.*, 1985, 922.



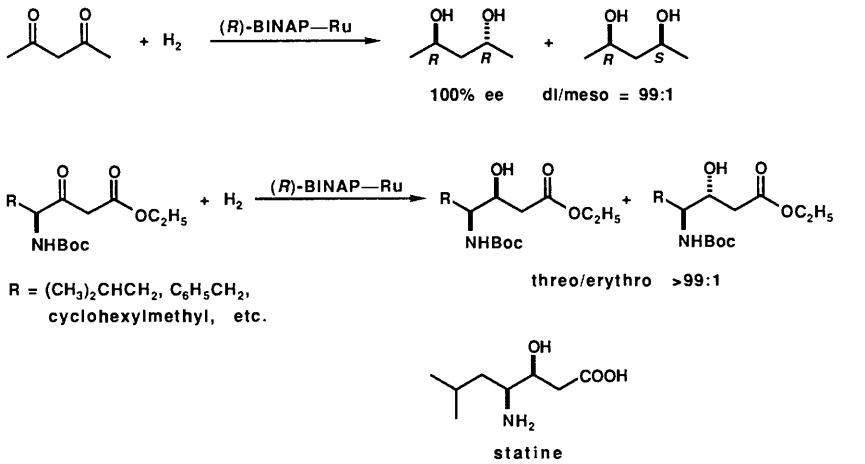
Scheme 10

yield, although unsubstituted acetophenone and the *m*- or *p*-bromo derivative failed to be hydrogenated in a satisfactory manner (Scheme 9).

This method is particularly useful for enantioselective access to β-hydroxy carboxylic esters which serve as important intermediates for natural product synthesis. A wide variety of prochiral β-keto esters having flexible structures are hydrogenated consistently in nearly quantitative yields and with extremely high (up to 100%) enantioselectivities.[23] Esters of methyl, primary, secondary, and tertiary alcohols as well as α-alkylated and α,α-dialkylated substrates were equally employable. Thus synthetic organic chemists no longer need envy bakers' yeast in this context (Scheme 10). This procedure allowed the first efficient chemical synthesis of GABOB and (*R*)-carnitine, a carrier of long-chain fatty acids through the mitochondrial membrane.[26] Hydrogenation of ethyl 4-chloro-3-oxobutanoate aided by the (*S*)-BINAP catalyst under the conditions effecting the reaction of 3-oxobutanoate in 99.4% optical yield (ethanol, room temperature, 100 atm, 10—40 h) afforded the desired (*R*)-hydroxy chloro ester in only $<70\%$ e.e. The inefficient enantiofacial differentiation is perhaps due to the competitive directing effect of the ester group and halogen atom present in the same molecule. However, a surprising chiral efficiency was obtained by the high-temperature, short-period reaction (100 °C, <5 min) affording the *R* enantiomer in 97% e.e. in 97% chemical yield. The same technique has been used for the synthesis of a component of compactin, an HMG-CoA reductase inhibitor (Scheme 10).

Double stereodifferentiation is a powerful mechanism to enhance a degree of

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



Scheme 11

stereoselection.[27] When prochiral, symmetrical β-diketones were subjected to the Ru catalysed hydrogenation, mixtures of *dl*- and *meso*-1,3-diols were formed (Scheme 11). The *dl*-isomers were dominant and their e.e.s were uniformly high. For instance, the reaction of 2,4-pentanedione catalysed by the (*R*)-BINAP catalyst proceeded by way of (*R*)-4-hydroxy-2-pentanone in 98.5% e.e., but the ultimate product was a 99:1 mixture of (*R*,*R*)-2,4-pentanediol in nearly 100% e.e. and (*R*,*S*)-2,4-pentanediol. The minor (*S*)-hydroxy ketone intermediate was washed away by intramolecular 1,3-chirality transfer, giving the *meso*-diol, and the calculated *R*,*R*/*S*,*S* ratio in the *dl*-type diol was *ca.* 900:1.[24] Diastereoselective hydrogenation of *N*-protected γ-amino, β-keto esters catalysed by the (*R*)-BINAP catalyst provides an efficient entry to statine, a key component of the aspartic proteinase inhibitor pepstatin.[28] The efficiency of the catalyst-to-substrate chirality transfer (catalyst control, >33:1) and the intramolecular 1,2-asymmetric induction (substrate control, 3:1) cooperate to form the natural *threo* series in >99:1 diastereoselectivity. A number of statine analogues are obtainable by this method using double asymmetric induction (Scheme 11).

Thus the present Ru catalysed hydrogenation exhibits wider scope than reactions with any other chiral transition-metal complexes so far designed. A range of optically active compounds of either chirality sense are now accessible, providing a versatile tool in stereoselective organic synthesis. This homogeneous hydrogenation procedure is superior to the heterogeneous version and compares well with the biochemical transformations, whose yields and enantioselectivities are often variable. The hydrogenation method is clean, operationally simple, economical,

[27] S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.
[28] T. Nishi, M. Kitamura, T. Ohkuma, and R. Noyori, *Tetrahedron Lett.*, 1988, **29**, 6327.

and hence is capable of conducting a large-scale reaction using high (up to 50%) substrate concentration.[29,30]

Now one may raise questions: (1) What is the major difference between the Ru chemistry and well-studied Rh catalysed hydrogenation? (2) Why does BINAP ligand work so effectively? The mechanism of the Ru–BINAP catalysed reaction remains to be elucidated. However, d^6 Ru^{II} chemistry differs from d^8 Rh^{I} chemistry distinctly. First, Ru^{II} complexes utilize higher co-ordination numbers, up to six in an octahedral structure, than Rh^{I} complexes which normally have a square planar geometry. Second, reaction of a Ru^{II} complex and with hydrogen generates Ru monohydride species[31] in contrast to the Rh promoted reaction occurring by way of the metal dihydride intermediate.[11] Such characteristics would reflect on the marked difference in reactivity–selectivity profiles in the hydrogenation. In the BINAP chemistry, the degeneracy caused by C_2 chirality of the diphosphine minimizes the number of the diastereomeric reactive intermediates and transition states. Flexible atropisomeric skeletal backbone of BINAP can produce a conformationally unambiguous metal chelate ring without concomitant increase of strain energy.[2] In addition, phenyl rings attached to the phosphorus atoms can suitably modulate stabilities of the intermediary complexes and transition states. Molecular structure of Ru–(*S*)-BINAP dipivalate complex determined by single crystal *X*-ray analysis is given in Figure 4.[14] The whole structure approximates C_2 chirality. The dissymmetry of (*S*)-BINAP fixes the delta conformation of the seven-membered chelate ring containing the diphosphine and Ru. This cyclic structure is highly skewed and this geometry in turn determines the chiral disposition of the phenyl rings on the phosphorus atoms; two phenyl substitutents are oriented in axial directions and the others in equatorial directions. These equatorial phenyl rings exert profound steric influence on the equatorial co-ordination sites of Ru. Consequently, the bidentate ligation of the pivalate moieties to Ru occurs stereoselectively, leading to exclusive formation of the Λ diastereomer. This diastereomeric differentiation of the two sets of quadrant space sectors is made in such a way as to avoid nonbonded interactions between the sterically demanding equatorial phenyl substituents and the carboxylate ligands. This is merely a ground-state structure of a catalyst precursor but, whatever the detailed reaction mechanism is, such an argument should also be applicable to the transition state or intermediates. Actual chemical transformations take place at the oxygen coordinated sites, and we believe that this is the steric origin of the high level of enantioselection. Stability of the transition structure (1) in the Rh–BINAP chemistry is also understandable in such a way.[8]

[29] R. Noyori, *Chimia*, 1988, **42**, 215.
[30] For related work, see: (*a*) ref. 25; (*b*) H. Kawano, Y. Ishii, T. Ikariya, M. Saburi. S. Yoshikawa, Y. Uchida, and H. Kumobayashi, *Tetrahedron Lett.*, 1987, **28**, 1905; (*c*) T. Tsukahara, H. Kawano, Y. Ishii, T. Takahashi, M. Saburi, Y. Uchida, and S. Akutagawa, *Chem. Lett.*, 1988, 2055; (*d*) H. Kawano, Y. Ishii, M. Saburi, and Y. Uchida, *J. Chem. Soc., Chem. Commun.*, 1988, 87.
[31] D. Evans, J. Osborn, J. A. Jardin, and G. Wilkinson, *Nature*, 1965, **208**, 1203.

Figure 4 *ORTEP drawings of* Λ-Ru[(*S*)-binap](OCO-t-C_4H_9)$_2$

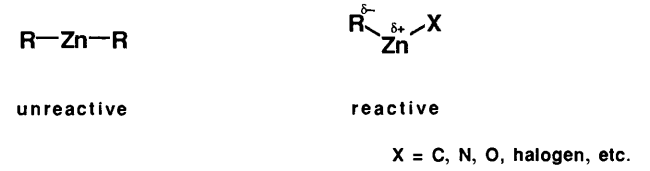


Figure 5

4 Asymmetric Alkylation of Carbonyl Compounds

Enantioselective alkylation of aldehydes by organometallic reagents is a fundamental problem in organic synthesis. Although there have been reports of several successful examples of this type of reaction,[32,33] a high degree of enantioselection is achievable by using a stoicheiometric or even excess amount of chiral auxiliary. Certain ligands may accelerate the nucleophilic alkylation but the difference in rates of the catalysed and uncatalysed reactions is not large enough to lead to a practical asymmetric catalysis.[32b] In this context, dialkylzincs, the oldest organometallic compounds, generate a variety of new, unprecedented chemistries, opening a novel domain of asymmetric catalysis. Monomeric dialkylzincs having a linear geometry are inert to carbonyl compounds but the structural modification by appropriate ligands or auxiliaries, forming a coordinatively unsaturated bent structure, increases the acceptor character of the Zn atom and donor property of the alkyl group, thereby increasing the reactivity toward carbonyl substrates (Figure 5). Here, some chirally well-designed auxiliary should also direct the stereochemical outcome in an absolute sense as well. Thus in the presence of a catalytic amount of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB), reaction of dialkylzincs and benzaldehyde in nonpolar solvents is accelerated markedly to give, after hydrolysis, the corresponding *S* alcohols in high (up to 99%) enantiomeric purity (Scheme 12).[34,35] Various *p*-substituted benzaldehydes and certain α,β-unsaturated and aliphatic aldehydes can also be alkylated with a high level of enantioselectivity. Dimethyl-, diethyl-, and di-n-butylzinc are employable as alkylating agents.

The catalytic cycle is illustrated in the scheme, where the DAIB structure is simplified.[36] Reaction of (−)-DAIB and dialkylzinc in a 1:1 molar ratio

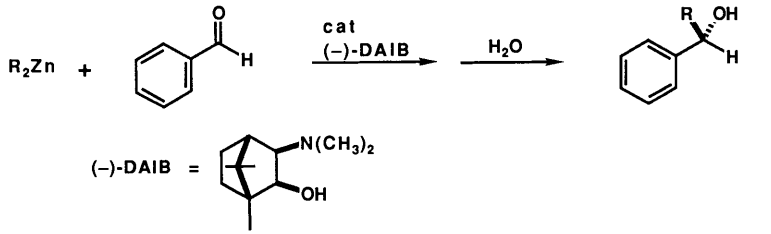
[32] (*a*) G. Soladié, in 'Asymmetric Synthesis', Vol. 2A, ed. J. D. Morrison, Academic Press, New York, 1983, Chapter 6; (*b*) J.-P. Mazaleyrat and D. J. Cram, *J. Am. Chem. Soc.*, 1981, **103**, 4585; (*c*) T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, *J. Am. Chem. Soc.*, 1979, **101**, 1455; (*d*) D. Seebach, A. K. Beck, S. Roggo, and A. Wonnacott, *Chem. Ber.*, 1985, **118**, 3673; (*e*) M. T. Reetz, T. Kukenhohner, and P. Weinig, *Tetrahedron Lett.*, 1986, **27**, 5711.

[33] R. Noyori, S. Suga, K. Kawai, S. Okada, and M. Kitamura, *Pure Appl. Chem.*, 1988, **60**, 1597.

[34] M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, 1986, **108**, 6071.

[35] Related works: (*a*) N. Oguni and T. Omi, *Tetrahedron Lett.*, 1984, **25**, 2823; (*b*) A. A. Smaardijk and H. Wynberg, *J. Org. Chem.*, 1987, **52**, 135; (*c*) K. Soai, A. Ookawa, K. Ogawa, and T. Kaba, *J. Chem. Soc., Chem. Commun.*, 1987, 467; (*d*) S. Itsuno and J. M. J. Fréchet, *J. Org. Chem.*, 1987, **52**, 4140; (*e*) P. A. Chaloner and S. A. R. Perera, *Tetrahedron Lett.*, 1987, **28**, 3013; (*f*) E. J. Corey and F. J. Hannon, *Tetrahedron Lett.*, 1987, **28**, 5233, 5237; (*g*) K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111; (*h*) W. Oppolzer and R. N. Radinov, *Tetrahedron Lett.*, 1988, **29**, 5645. See also, D. A. Evans, *Science*, 1988, **240**, 420.

[36] M. Kitamura, S. Okada, S. Suga, and R. Noyori, *J. Am. Chem. Soc.*, in press.



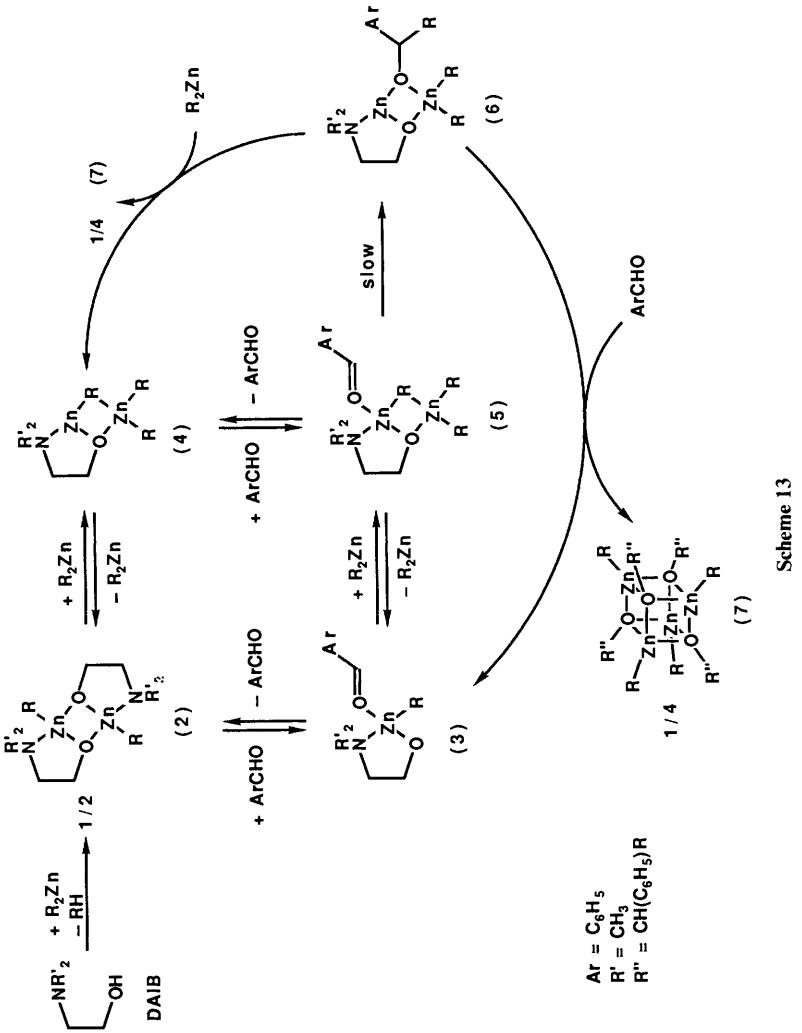
Scheme 12

produces a single Zn chelate complex (2), which does not alkylate benzaldehyde but acts as catalyst precursor. Significantly, the alkylation proceeds *via* a dinuclear Zn species (5) containing DAIB auxiliary, aldehyde ligand, and three alkyl groups. The resulting bridged alkoxide (6), upon exposure to benzaldehyde or dialkylzinc, undergoes instantaneous decomposition to the stable cubic tetramer (7), regenerating (3) and (4), respectively (Scheme 13). Under the catalysis conditions, complexes (2)—(5) are equilibrating on a soft energy surface, consistent with the fact that, when two different dialkylzincs are used, a statistical distribution of the possible products is obtained regardless of the order or way of mixing the two alkylzincs. Here, only relative reactivity of alkyl groups is important. Kinetic measurements and temperature effects on the enantioselectivity indicate that the alkyl transfer process, (5) ⟶ (6), is the turnover-limiting and stereo-determining step.

The DAIB-aided enantioselective alkylation exhibits enormous nonlinearity in terms of optical purity of the chiral source and alkylation products.[33,36–38] Typically, when benzaldehyde and diethylzinc are reacted in the presence of 8 mol % of (−)-DAIB in 15% e.e. in toluene, (*S*)-1-phenylpropyl alcohol is produced with 95% e.e., a value close to 98% obtained using enantiomerically pure DAIB. The nonlinear effect is clear in Figure 6 which shows the e.e.s of (*S*)-products as a function of the e.e. of (−)-DAIB. Under certain conditions, turnover efficiency of the chiral catalyst system is >600 times greater than that of the coexisting achiral catalyst system. This unusual phenomenon is a result of a marked difference in chemical properties of the diastereomeric dinuclear complexes formed from dialkylzincs and DAIB. Reaction of equimolar amounts of dimethylzinc and enantiomerically pure (−)-DAIB affords a dinuclear chelate complex with C_2 chirality, which dissociates readily to catalytically active monomeric species. By contrast, dimethylzinc and racemic DAIB generate a more stable, but much less reactive dinuclear complex possessing *meso*-C_i structure rather than a racemic mixture of the chiral complexes. Molecular structures of these complexes determined by single crystal *X*-ray analyses are illustrated in Figure 7.[36]

[37] N. Oguni, Y. Matsuda, and T. Kaneko, *J. Am. Chem. Soc.*, 1988, **110**, 1877.

[38] (*a*) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, and H. B. Kagan, *J. Am. Chem. Soc.*, 1986, **108**, 2353; (*b*) C. Agami, J. Levisalles, and C. Puchot, *J. Chem. Soc., Chem. Commun.*, 1985, 441.


DAIB
+ R2Zn
– RH
1/2
(2)
+ R2Zn
– R2Zn
(4)
1/4
(7)
R2Zn
– ArCHO
+ ArCHO
(3)
(5)
slow
(6)
ArCHO
1/4
(7)
Ar = C6H5
R' = CH3
R'' = CH(C6H5)R

Scheme 13

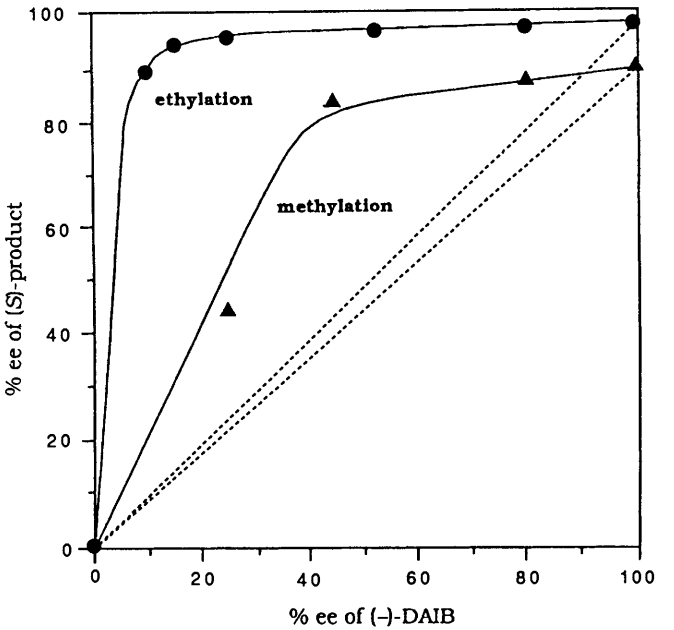
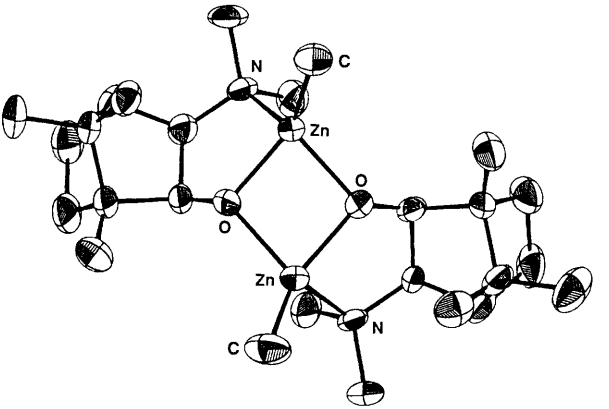


Figure 6 *Correlation between the e.e. of the alkylation product and the e.e. of the chiral auxiliary.* ● *Reaction using* 0.42 M $(C_2H_5)_2Zn$, 0.42 M C_6H_5CHO, *and* 34 mM (−)-DAIB *in toluene at* 0 °C. ▲ 0.47 M $(CH_3)_2Zn$, 0.49 M C_6H_5CHO, 47 mM (−)-DAIB *in toluene-*d_8 *at* 32 °C

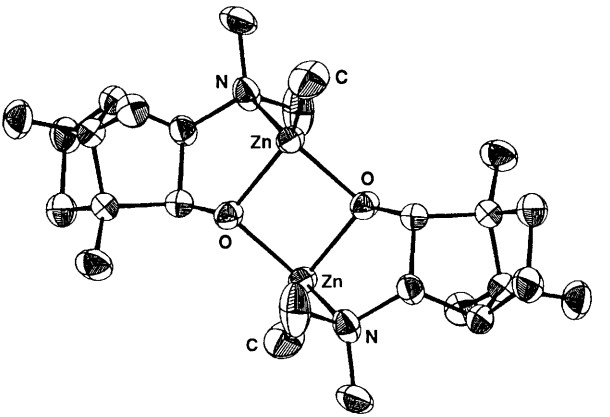
Alkyl transfer from the mixed ligand complex (5) is conceived to occur *via* a folded bicyclic transition state (8) featuring a tricoordinate structure of the migrating R group. The kinetic bias leading to the *S*-configurated alkoxide derives primarily from a nonbonded repulsion between the carbonyl substrate (Ar and H) and a terminal R group attached to Zn_B atom.

Organometallic chemistry of homo- or hetero-multinuclear compounds is increasing the synthetic importance, and the nonclassical dinuclear mechanism, which has been theoretically advanced,[39] can provide reasonable explanations for various stereoselective reactions. In order to create a single reactive species, we designed binaphthol-modified Li/Mg binary organometallic reagents having empirical formula of (9) and found that they undergo stoicheiometric enantioselective alkylation with aldehydes (Scheme 14) to give the corresponding secondary alcohols in high e.e.s.[33] For example, 1-phenylpropyl alcohol was produced in up to 92% e.e. The possible transition state resulting in the *S*/*S* auxiliary/alcohol asymmetric induction is illustrated by the structure (10) (S = solvent; naphthalene rings are omitted in (10a)). Chiral reducing agent, BINAL-

[39] A planar bicyclic transition state has been proposed for reaction of methyllithium dimer and formaldehyde: E. Kaufmann, P. von R. Schleyer, K. N. Houk, and Y.-D. Wu, *J. Am. Chem. Soc.*, 1985, **107**, 5560.

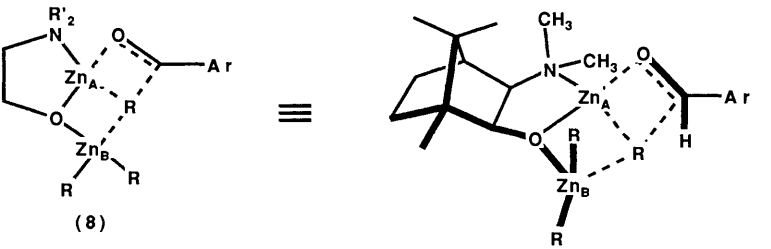


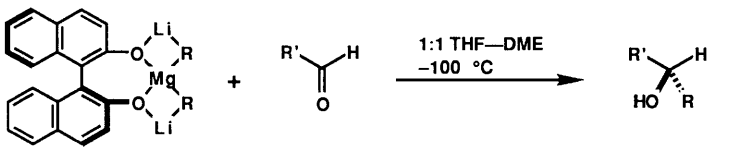
C_2 **reactive**



C_i **unreactive**

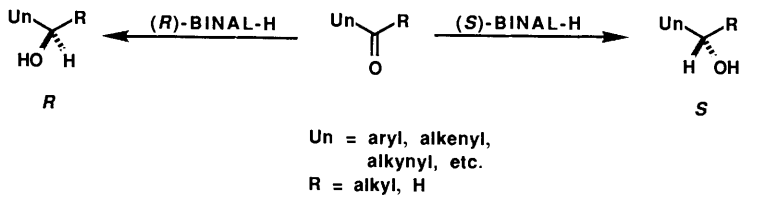
Figure 7 *ORTEP drawings of complexes formed from equimolar amounts of dimethylzinc and (−)-DAIB (upper) and dimethylzinc and (±)-DAIB (lower)*





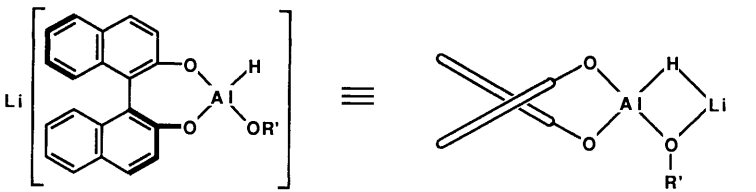
(9)

Scheme 14

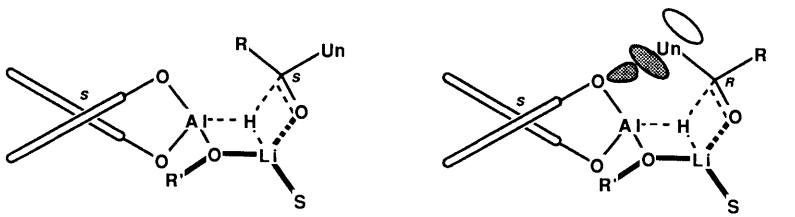


R *S*

Un = aryl, alkenyl, alkynyl, etc.
R = alkyl, H



(*S*)-BINAL-H

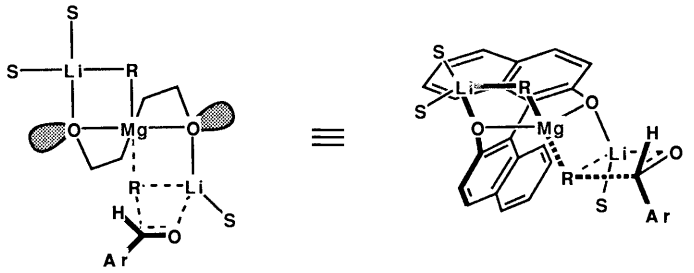


(11) (12)

Scheme 15

H, exhibits exceptionally high enantioface-differentiating ability in the stoichiometric reduction of prochiral ketones having an aromatic, olefinic, or acetylenic substituent.[40] With many carbonyl substrates, e.e.s greater than 90% are obtainable, where the enantioselection is governed primarily by electronic factors. Now a new model is presented to explain the general binaphthol/carbinol

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



(10a) (10b)

configurational relationship (*S*/*S* or *R*/*R*), which is independent of the relative bulkiness of unsaturated and alkyl groups flanking the carbonyl moiety. In the (*S*)-BINAL-H reduction, the *S*-generating transition structure (11) is favoured over the diastereomeric *R*-generating structure (12), because the latter is configurational relationship (*S*/*S* or *R*/*R*), which is independent of the relative bulkiness of unsaturated and alkyl groups flanking the carbonyl moiety. In the (*S*)-BINAL-H reduction, the *S*-generating transition structure (11) is favoured over the diastereomeric *R*-generating structure (12), because the latter is destabilized by the substantial n/π type electronic repulsion between a binaphthoxyl oxygen and the unsaturated moiety. The oxygen/R steric repulsion in (11) becomes significant by increasing the bulkiness of R but cannot overcome the overwhelming electronic influence (Scheme 15).

5 Epilogue

The development of homogeneous asymmetric catalysis using chiral metal complexes has provided the straightforward solutions to many challenging problems, proving the validity of the chemical conception. I would conclude that asymmetric catalysis is a four-dimensional chemistry which consists of two fundamental elements in Nature; chirality and circularity. High efficiency is obtainable by creation of ideal three-dimensional structures (*x*,*y*,*z*) coupled with appropriate kinetics (*t*). This is a frontier of organic chemistry full of promise.[1]

Acknowledgements. It is with much pleasure that I acknowledge my collaborators in the successful development of a range of highly stereoselective organic reactions which are described herein. Names of the individuals who made the sustained intellectual and experimental efforts are given in the references. I have particularly enjoyed collaborations in BINAP chemistry with the research groups headed by Professors H. Takaya (Institute for Molecular Science, Kyoto University), S. Otsuka (Osaka University), and Dr. S. Akutagawa (Takasago Research Institute). I am also grateful for the financial support of the Ministry of Education, Science, and Culture of Japan (Specially Promoted Research No. 62065005).