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# Review
# Some Remarks on Asymmetric Syntheses from Recent Studies

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## Summary

Some asymmetric syntheses were presented here and discussed briefly including NADH model reactions, phase transfer-catalyzed asymmetric epoxidation, enantiotopic group-selective hydrolysis of a malonic anhydride with alkoxide anion, intramolecular acid-catalyzed lactonizations, catalytic asymmetric Diels-Alder synthesis, asymmetric aldol condensation, chiral homoallyl alcohol synthesis, asymmetric addition of diethylzinc to aldehyde, kinetic resolution of racemic hydroperoxides and binaphthol by lipase, and lipase-catalyzed enantiotopic group differentiation of 2-O-benzylglycerol and 2-alkylpropanediol.

## Introduction

A considerable development in asymmetric synthesis has been achieved after its long history aiming at invention of new system, search for new stereochemical controlling factor and exploitation of methods for highly stereoselective synthesis particularly for biologically active materials as well as medicines. Needless to say is that medicinal compounds directly affect to our lives with salutary or dangerous way or with no effect depending on their sense of stereochemistry. For example, (*R*)-form of thalidomide has sedative action but its (*S*)-form is strongly teratogenic. Also, (+)-form of esteron, peniciline G and prostaglandine $F_{2\alpha}$ have female hormon, antibacterial and uterine contraction activity respectively. Their (−)-forms, however, have no such activity[1]. Diacylglycerol is known to be an essential component for activation of protein kinase C in the presence of calcium ion and phosphatidyl serine. In this process, it was shown that the diacylglycerol activation effect was stereospecific, with only the 1,2-*sn*-diglycerides being active and its antipode 2,3-*sn*-form, not[2]. It should be noted that such an experiment serves to infer whether the diacylglycerol interacts simply with bulk lipid(s) non-specifically or interacts in a stereospecific manner with protein kinase C.

In the long history of asymmetric synthesis, many techniques have been exploited including a number of studies which showed remarkably efficient and high stereoselectivity. This field, however, awaits further studies for new strategy, more convenient procedures and low cost of materials. Of course, there still remain many organic reactions which should be extented to asymmetric syntheses. Although, at present, we can not predict right answer how we can achieve very high stereoselectivity for each asymmetric reaction, it may be worthy of note to describe the following factors or conditions as a general guide to the problem.

* Cyclic structure of reactants and/or transition states.
* Intramolecular process.
* Concerted reaction.
* A system involves hydrogen bonding(s), elecrostatic interaction(s) and chelation(s) with metal speices for stereochemical control.
* Proximity of chiral center(s) to reaction site(s).
* Control of reaction temperature.

* Right selection of reaction medium.
* Restriction of space by steric factors for an approach of reagent to substrate.
* Introduction of $C_2$-symmetry into reagents and/or catalysts.
* Choice of non-equilibrium reaction and/or reaction conditions.
* Avoiding secondary effects of reaction product(s) on the major stereochemical course.
* Molecular structure of reactants should be flexible enough to form conformationally homogeneous transition state.

Of course, it is not neccessary to fulfil all of these conditions and some of them may be negative effect(s) on some cases. It requires right selection, right combination and subtle control of above conditions for each reaction. Furthermore, new ideas are always expected for new reactions as well as existing ones to be improved for their enantiomeric excess(e.e.). In fact, there remain a number of chemical reactions which are difficult to perform them with high stereoselectivity. Therefore, even at the present time, chemical intuitions are still very much to the for in developing new and highly efficient systems. Along this line, the present short account will introduce some asymmetric reactions conducted by us in recent years as well as very recent topics in this field by other investigators. Review articles which cover recent advances of asymmetric synthesis are listed in references[3].

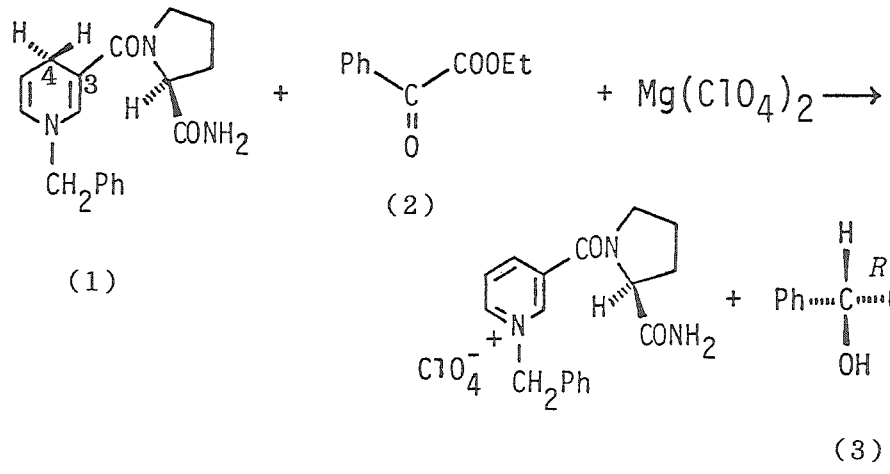
## Asymmetric Reductions with Chiral NADH Model Compounds

Among many enzymes, the pyridine nucleotide-dependent oxidoreductases have attracted organic chemists attempting to elucidate the nature of hydrogen atom transfer between substrates and the coenzyme as well as to simulate enzymatic process in simplified nonenzymatic systems. A number of studies have been made in the hope of understanding the stereochemical picture of the hydrogen transfer by dehydrogenase-catalyzed reactions[4]. The potential for asymmetric reduction in organic synthesis by use of simplified NADH model compounds has also been obtained by us.

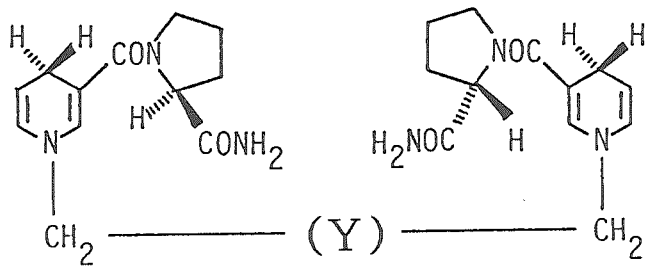
An amino acid, L-proline has been noted to be a good candidate as chiral auxiliary because of its rigid cyclic structure[5]. In our NADH model system too, the amino acid was jointed to the dihydropyridine via amide bond and the carboxyl group of proline moiety was transformed to amide function expecting efficient chelation with magnesium ion as catalyst and substrate, ethyl benzoylformate. Thus designed and synthesized was a model compound (1) which was submitted to the asymmetric reduction of ethyl benzoylformate[6]. The reaction was conducted in dry acetonitrile at room temperature in the presence of half molar amount of magnesium perchlorate and the product ethyl mandelate was obtained in 83%e.e. which is much higher than those attained with dihydropyridine reductants carrying other amino acids including L-alanine[7]. Thus, by the replacement of acyclic amino acid to L-proline, considerable increment of stereoselectivity was achieved and it could be ascribed to the introduction of cyclic structure as well as two amide functions on the dihydropyridine nucleus.

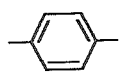
As an extension of the above system, two molecules of prolinamide derivative of dihydropyridine were linked through their $N_1$-substituent with $p$-xylylene- or hexamethylene bridge [models (4) and (5)]. These reductants were prepared particularly so as to introduce $C_2$-symmetry in the structure[8].

When the NADH model compound (4) or (5) was submitted to the reduction of ethyl benzoylformate in the presence of equimolar amount of magnesium perchlorate in dry acetonitrile at room temperature, very high enantioselectivity ($\simeq$98%e.e.) was attained. Worthy of note were the facts that : (i) when ortho- or meta-xylylene bridge was applied [models (6) and (7)], an abrupt decrease of the stereoselectivity to 34-36%e.e. was observed ; (ii) When the relative concentration of magnesium perchlorate was increased to equimolar amount of the model, the e.e. increased monotonically. Under higher concentrations of the magnesium ion, however, the e.e. was kept constant and no decrease was observed. This feature exhibits a



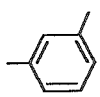
(1) (2) (3)



(4): Y= 

(5): Y= $-(CH_2)_4-$

(6): Y= 

(7): Y= 

striking contrast to the case with model (1) where maximum e.e. was obtained when 0.5 molar equivalent of magnesium perchlorate was used[6]. This result indicates that a 1 : 1 complex between $Mg^{++}$ and the bis-model (4) was formed in the solution. Spectral evidence showed that magnesium ion complexes to the primary amide carbonyl oxygen of the prolinamide moiety. It then seems likely that the operating species of the bis-model reductants assume a $C_2$-conformation with the specific faces of the two juxtaposed equivalent dihydropyridine nuclei disposed toward the outside for the attack on substrates and a $C_2$ axis passing through the interposing magnesium and the center of *p*-xylene bridge (Fig. 1). Thus, the bis-model furnish the substrate with a chiral environment such that only one of the diastereotopic hydrogens is of necessity available for transfer at either side. In this system, therefore, cyclic structure of the prolinamide and the reductant species (Fig. 1), spatial restriction of the substrate approach by means of chelation control as well as $C_2$-symmetry may be of primary importance for the observed high stereoselectivity.

Among them, metal ion-amide bond attractive interaction(s) in particular seems to be of potential role for making effective chiral environment around the reaction site (either of the two hydrogens at 4-position of the dihydropyridine). An another feature of these systems in-

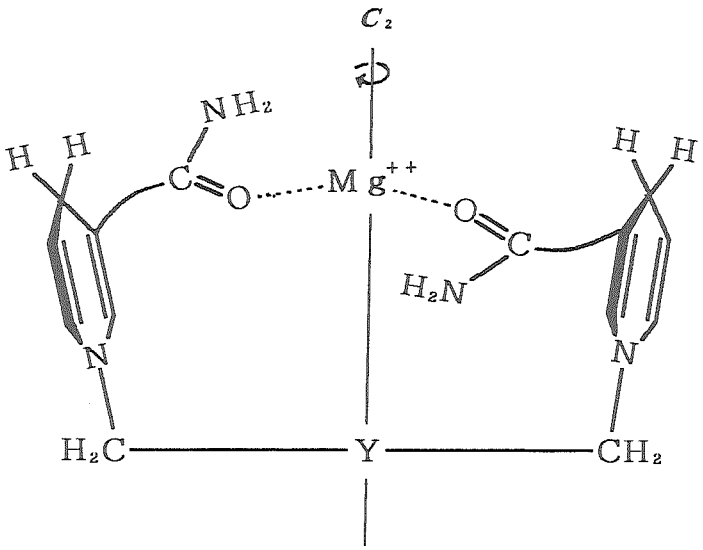



Fig. 1 $C_2$-Symmetric reductant species of the models (4) and (5)

volving chirality of L-prolinamide fixed at the 3-position of the dihydropyridine nucleus in both cases is that all the product ethyl mandelates were found to have (*R*)-configuration irrespective of reaction conditions and changes in reductant structures. Accordingly, it was assumed that if the prolinamide moiety was alienated from the reaction site by long bridge as shown in the model (8), configurational reversal (from *R* to *S*) of the product mandelate might be observed by any chance[9]. Against the expectation, however, the product was found again to have the same (*R*)-configuration. Of unexpected interest, however, was facts that considerably high enantioselectivity (90% e.e.) was recorded with this model despite the long separation by ten atoms between the chiral center and the reaction site. A reasonable explanation for this high selectivity could be provided by an assumption that the prolinamide moiety should reside in close proximity to the reaction site as represented by Fig. 2[10]. By this framework, the prolinamide not only induces a chiral environment around the reaction site but also restricts the substrate approach to one side of the dihydropyridine ring opposit to the prolinamide moiety. Some data were obtained indicating that such mechanism was operating.

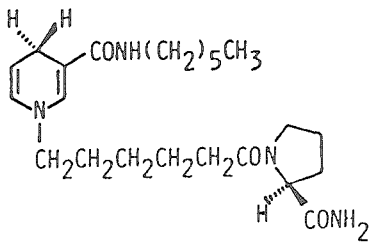
(i) In the $^{13}C$ NMR spectra of the model (8), the chemical shifts of the three kinds of amide carbonyl carbons are moved significantly (0.71-3.45 ppm) to lower fields on addition of equimolar magnesium perchlorate.

(ii) In the presence of equimolar magnesium perchlorate, circular dichroism was recorded at 350 nm which is a characteristic absorption band of dihydropyridine. Without the magnesium salt, however, no CD spectrum was observed at all.

(iii) When the model compound (9) in which an ester group was introduced in the substituent at 3-position was used, the stereoselectivity dropped to only 3-5% e.e.

(iv) Significant e.e. (26%) was observed from a reaction of achiral dihydropyridine (10) with ethyl benzoylformate in the presence of equimolar amount of a chiral fragment (11) and the same amount of magnesium perchlorate.

Thus, central role of magnesium ion-amide interaction(s) were manifested by these observations. In this system too, proximity of chiral center to the reaction site by chelation control are deeply responsible for the high stereoselectivity.



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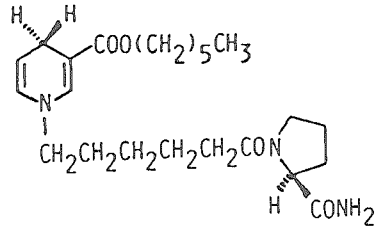

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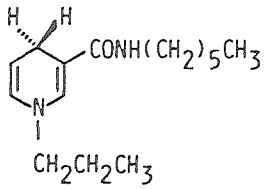

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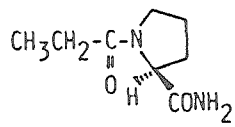

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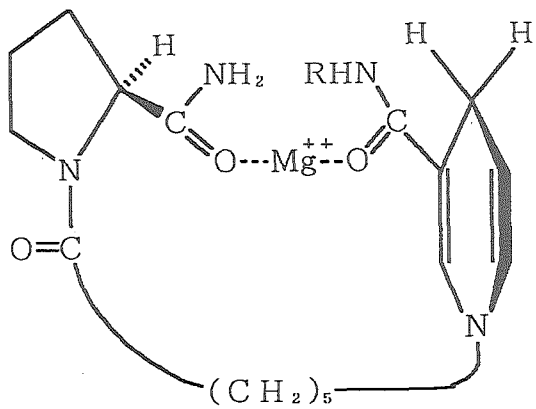
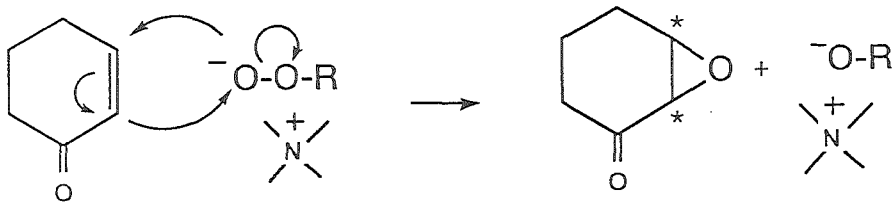


Fig. 2 Assumed reductant species of the model (8)

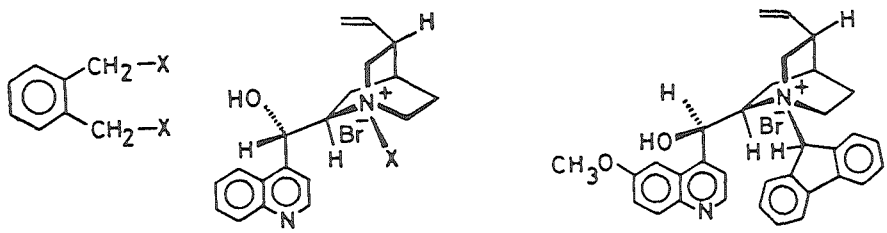
## Strategies for Asymmetric Inductions from Recent Examples

Although various ideas and strategies for asymmetric synthesis have been found in a number of chemistry journals, most approches have been emphasized on creations of novel and highly efficient chiral auxiliaries and catalysts based on stereochemical concepts. As described in the introduction, however, it still relies heavily on our chemical intuition in addition to many informations piled up so far by forerunners. In this regard, an example was cited here in which steric factors contributed to a considerable extent for control of stereochemical course[11].

In the presence of hydroperoxide anion paired with quaternary ammonium cation (13) as a phase transfer catalyst (PTC), it is known that epoxidation of cyclohexenone (12) proceeds giving an epoxide (14) by hydroperoxide such as hydrogen peroxide, tert-butylhydroperoxide in



(12) (13) (14) (15)



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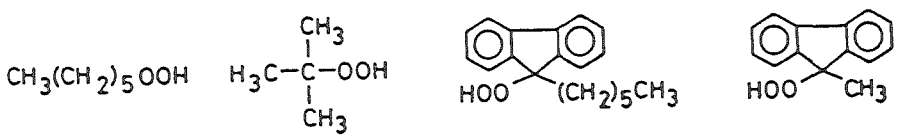
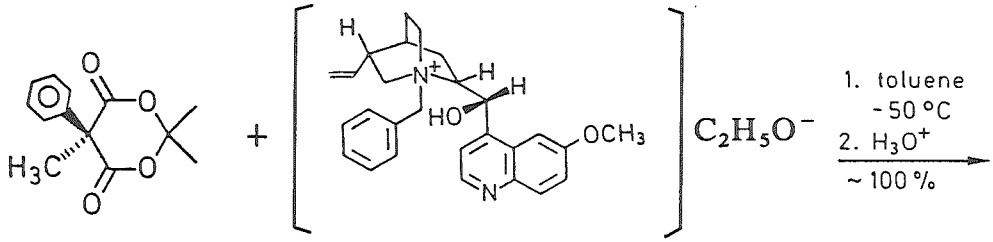


(18) (19) (20) (21)

an alkaline conditions. For this system, by use of a bis-type cinchonium bromide (16) as a chiral PTC, and hexylhydroperoxide (18) as an oxidant, only 4%e.e. was observed in the product cyclohexene-2,3-epoxide, and tert-butylhydroperoxide (19) afforded 33%e.e. On the other hand, with fluorenyl hydroperoxide (20) or (21), the stereoselectivity was much improved to 61%e.e. In addition to this experiment, model changes of PTC itself were also examined. When fluorenyl group was introduced to cinchonine giving an another chiral PTC (17) and used in the same epoxidation with tert-butylhydroperoxide, 61%e.e. was attained which was much improvement compared to 33%e.e. by the use of bis (PTC) (16) and the same hydroperoxide. Thus, this study constitutes a first example where planar fluorenyl group affects stereochemical environment of reactants and catalyst to considerable extents, and this approach using fluorenyl group should be of some use in other system, too.

Naturally occuring cinchona alkaloides (quinine, quinidine, cinchonine, cinchonidine and their epimers have frequently been used as a chiral auxiliary[12] since they have rigid molecular framework with ring structures as well as hydroxy- and nitrogen functional groups which have been considered to provide ideal asymmetric environment. Viewing from this, one of our study was cited here[13].

This asymmetric synthesis involves enantiotopic group differentiation between pro-*R* or pro-*S* carbonyl group of a malonic anhydride (22) in the ring opening reaction by ethoxide anion as a nucleophile paired with chiral N-benzylcinchoninium cation (23). The alkoxide was prepared

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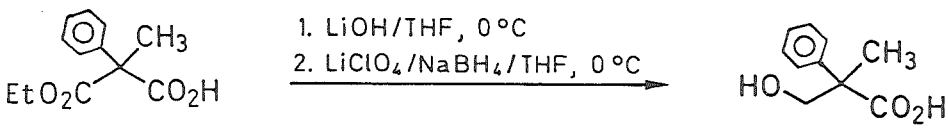


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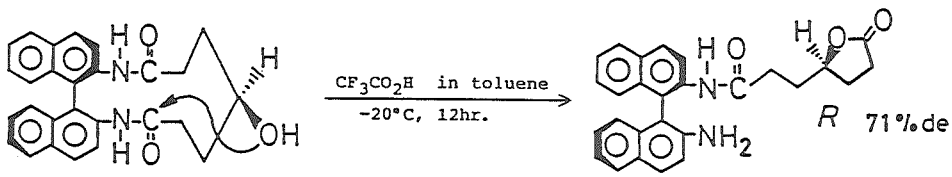


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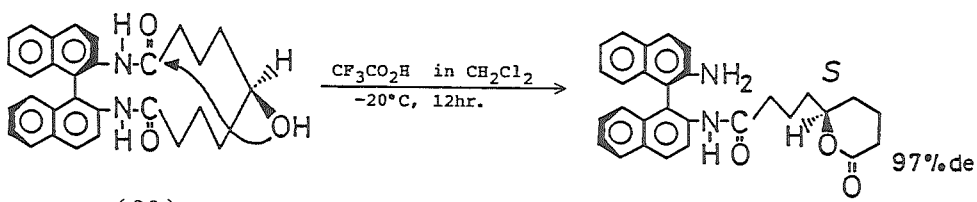


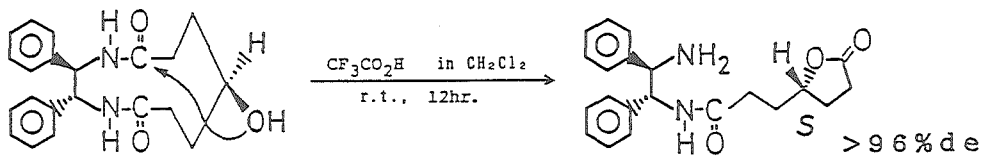

(28) (29)

in situ and submitted to the reaction with the substrate (22) at −78°C giving (*S*)-2-methyl-2-phenylmalonic acid monoethylester in 45% e.e. with 90% chemical yield. This half ester could easily be transformed to α-methyltropic acid. Although the stereoselectivity still remains to be improved, this system constitute a new route to chiral malonic acid derivatives via enantioselective ring-opening of cyclic acylal such as (22) with alkoxide anion by use of cinchona alkaloids.

Strategies based on enantiotopic group differentiation reaction described above as an example has become a progessing area of asymmetric synthesis in recent years[14]. Viewing from this feature, following examples will deserve describing here. Cyclic diamides (26) and (28) bearing chiral (*R*)-binaphthyldiamine and a hydroxyl group have been so designed that, by treatment with acid, general acid-catalyzed intramolecular nucleophilic attack of the hydroxyl group on either of the enantiotopic carbonyl groups might occur in a stereospecific manner being dependent on the $C_2$-chirality provided by the diamine moiety. Thus, when the hydroxydiamide (28) was treated with trifluoroacetic acid in dichloromethane at −20°C, δ-lactoneamide (27) with

(*R*)-configuration at the carbon atom in the lactone ring was obtained with almost complete diastereoselectivity. On the other hand, the same acid treatment of (26) afforded γ-lactonamide with 71%d.e. Thus, despite the use of the same binaphthyldiamine, the difference in the ring size was found to cause the change in diastereoselectivity to a considerable extent and even the configurational reversal of the newly created asymmetric carbon atom[15]. So far as δ-lactone formation, however, this system was proved to be an excellent method in respect of stereoselectivity.

In due course, to make superior system for optically active γ-lactone formation, we replaced the binaphthyldiamine moiety to optically active (*R*, *R*)-1,2-diphenylethylenediamine which was also $C_2$-symmetric but not aromatic amine and rotationally more flexible than binaphthyldiamine[16].

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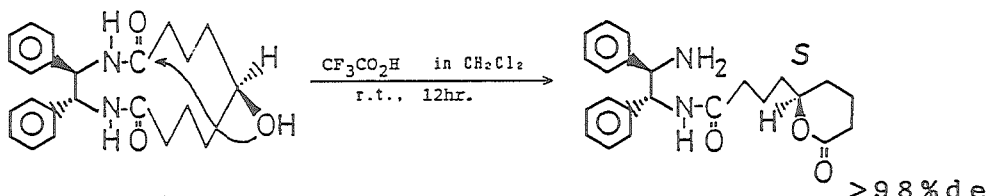


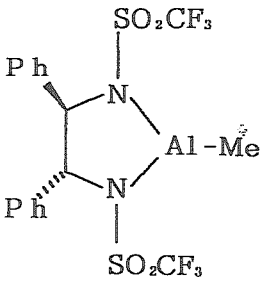

(32) (33)

By the treatment of cyclic diamines (30) and (32) with trifluoroacetic acid in dichloromethane lactonizations proceeded smoothly at room temperature affording lactonamides (31) or (33) in 82 and 79% chemical yields respectively. Proton NMR spectrum (200 MHz) of (31) clearly demonstrated that the asymmetric carbon on the lactone ring had (*S*)-configuration with more than 96%e.e. in a range of NMR noise level. This result also indicated that pro-(*S*) carbonyl of (31) was attacked preferentially by the hydroxyl group. Similarly, the asymmetric carbon on the lactone ring of (33) had (*S*)-configuration with more than 98%e.e. as shown by 400 MHz proton NMR. Of particular interest was a fact that the replacement of binaphthyldiamine to 1,2-diphenylethylene diamine realized a significant increase of diastereoselectivity (71-96%e.e.) in the formation of the γ-lactone and this result might be ascribed to the rotationally more allowed flexibility of the C-C bond in the 1,2-diphenylethylenediamine moiety. The high stereospecificities recorded by the present system are largely due to the cyclic structure as well as intramolecular process.

Very recently, by use of modified 1,2-diphenylethylenediamines, highly efficient asymmetric synthesis has been exploited by E. J. Corey et al[17]. Structures of the three derivatives prepared were (34), (35) and (38) all of which have $C_2$-symmetry. First, the authors conducted asymmetric Diels-Alder reactions of cyclopentadienes and optically active menthol acrylate or achiral crotonic acid amide as a dienophile in the presence of a chiral Lewis acid catalyst (34) and obtained the adduct in high enantiomeric excess. Particularly, the reaction of benzyloxymethylcyclopentadiene with the crotonic acid amide afforded the product (36) in 88% chemical yield and 94%e.e. The authors furthered the application of this chiral auxiliary system to asymmetric aldol condensations. In the presence of (*R*, *R*)-(35), carboanion from diethyl

ketone added smoothly to propionaldehyde giving the adduct (37) in 91% chemical yield with syn-form of more than 98% and the e.e. exceeded to 98%. It was pointed out that the product (37) was known to be the rice and corn weevil aggregation pheromone called sitophilure.

The third example published successively by Corey et al. is an enantioselective alkyllation of aldehyde[18]. In this case, 1,2-diphenylethylenediamine derivative (38) was prepared as a chiral allyl donor. When the reagent was submitted to the reaction with several aldehydes, the authors obtained homoallylalcohols (39) with 90-98%e.e. For these highly selective re-

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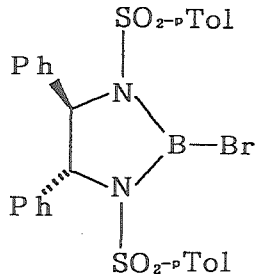


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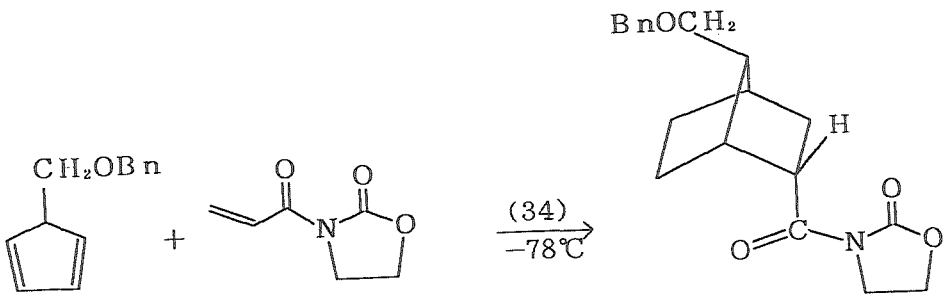


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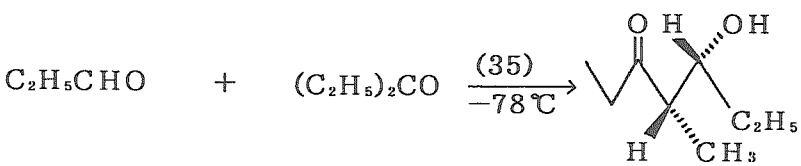


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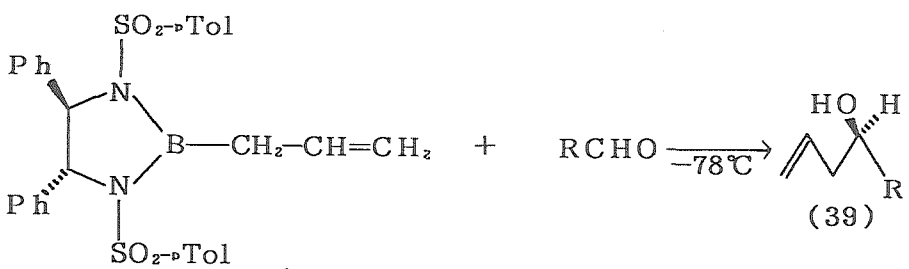
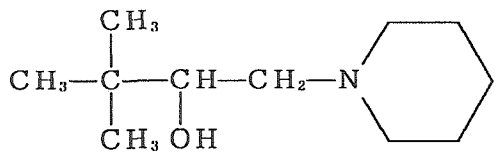


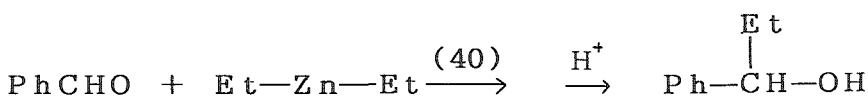

(38) (39)

actions, the authors proposed transition state structures in which aluminum or boron atom-carbonyl oxygen electronic interactions played a central role for making rigid homogeneous transition state. It appeared that $C_2$-symmetry of those catalyst or reagent may also be responsible for the high stereoselectivity.

Highly efficient asymmetric carbonyl alkylation by dialkylzinc in the presence of optically active aminoalcohol as a chiral auxiliary has recently been developed by several research groups[19]. In this system, Oguni et al. conducted the alkylation of benzaldehyde with diethylzinc at −10°C in the presence of 2 mol% of 1-piperidino-3,3-dimethyl-2-butanol (40) having 20% optical purity rather than optically pure form. Supprisingly, the product alcohol (41) was found to have 88%e.e. with (*R*)-configuration[20].



(40)



(41)

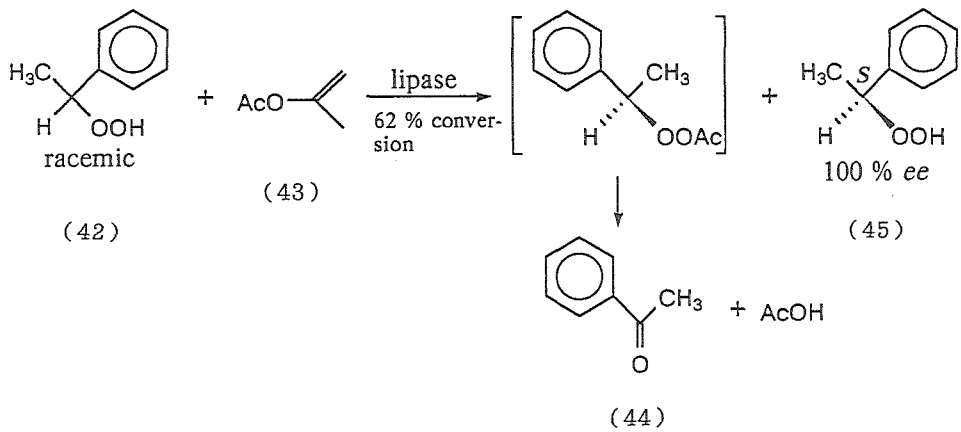
In a mechanism proposed by the authors involves a catalytic cycle in which the zinc-amino-alcohol complex form dimers. Particular important is a fact that the dimer composed of (*R*)- and (*S*)-monomer (meso-dimer) is more stable in a solution than that from two (*R*)-monomers or two (*S*)-monomers. Accordingly, only the latter dimer can form a second complex with diethylzinc and this complex is reactive to prochiral aldehyde. Therefore, if the aminoalcohol is partially racemic, the less enantiomers form the meso dimers with the equal amount of its antipodes leaving one enantiomer molecules which makes (*R*)-(*R*) or (*S*)-(*S*) dimer. By this way, optical concentration of the catalyst is attained and then stereoselective asymmetric addition reaction occurs thereby in a catalytic manner performing the asymmetric amplification[20b].

## Enzymatic Approaches for Asymmetric Syntheses of Optically Active Compounds

The usefulness of enyzymes as bio-catalysts in organic reactions have been increasingly recognized in recent years and the progress is very rapid. The reasons for the rapid progress are due to the discoveries that (i) some enzymes have very broad substrate specificity and (ii) even in organic media, some enzymes can work very well as a bio-catalyst with comparable or higher efficiency and selectivity. Therefore, it is worth presenting some examples here. Several excellent reviews will serve well for our better understanding of the whole area of this field[21].

While general conditions for higher stereoselectivity in asymmetric synthesis have been described in the Introduction, most of them, unfortunately, can not be extended so far as to enzymatic reactions[22]. Among them, however, irreversibility of the enzymatic reaction, right selection of the reaction medium[23] and screenings of best enzymes are still very important[22,23,24].

Among many enzymes, lipases have been recognized well as one of the most vasatile enzymes because of their vast substrate specificity, high stability and easy availablility as well as high stereoselectivity[21]. This nature of the enzyme allowed various hydrolytic reactions in aqueous solution as well as ester exchange and ester synthesis in organic media. One particular feature of new developments in lipase catalyzed reaction is concerned with unnatural substrates whose chemical structure are much different from glycelides. We present here a special case of an unnatural substrate. For example, no reaction takes place for a racemic hydroperoxide (42)

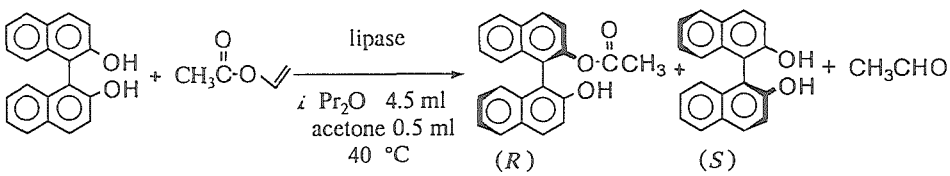



in cyclohexane by an action of isopropenyl acetate (43), a strong acetylation agent. However, by an addition of Pseudomonas fluorescens lipase to the solution, acetylation of the hydroperoxide proceeded smoothly giving acetophenone (44) since it is known that acetylated primary and secondary hydroperoxide is very unstable and immediately decompose to aldehyde or ketone respectively. When, the lipase catalyzed reaction was quenched at 62% conversion by simple filtration of the enzyme and from the filtrate unreacted hydroperoxide (45) was recovered and purified[25]. The hydroperoxide thus obtained was found to be optically pure (100% e.e.) with (*S*)-configuration. Thus it was found for the first time that lipase could catalyze acetylation of hydroperoxy group as well and the reaction was very stereoselective. From additional experiments, the e.e. of the unreacted hydroperoxides was found to be strongly dependent on the extent of reaction conversion as was characteristic of kinetic resolution. The e.e. of the unreacted 1-phenylethyl hydroperoxide increased from 71 to 100% when the conversion was raised from 49 to 62%. Significantly, although the reaction site oxygen is separated from the asymmetric carbon by one oxygen atom in the structure of all the hydroperoxide, very high enantiomer enrichments were attained by the lipase-catalyzed kinetic resolutions. While pig pancreatic lipase catalyzed as well the acetylation of 1-phenylethyl hydroperoxide in cyclohexane, the enantioselectivity was found to be low (16% e.e.). With regard to reaction medium, isopropyl ether could also be used, however, the reaction mixture colored and the enantioselectivities were lower than those obtained in cyclohexane. Particular noteworthy was a fact that the lipase recovered from the reaction mixture still retained full activity for the same substrate with the same enantioselectivity. This result indicated that the lipase was quite stable under such stongly oxidative conditions as imposed by the substrate itself. A report has been published[26] recently which described that *Pseudomonas fluorescens* lipase suffers some inhibition and inactivation by fat peroxide in batch and continuous glycerolysis. In relevant to this, our finding about the stability in organic solvent is of particular interest but await further experimental verification for this reason.

On the other hand, synthesis of chiral hydroperoxide has been challenged[27] for about 40 years

as an arduous chemical problem and a variety of methods have been developed, most of which based on configurational reversal of optically active halogenide or methansulfonate of optically active alcohols via nucleophilic substitution of hydroperoxide anion. Some other methods have been exploited including HPLC separation of diastereomeric perketals derived from racemic hydroperoxides and chiral isopropenyl ether[28]. However, existing methods are still not ideal because of their some drawbacks and limitations. From this view, the present enzymatic method appeared to be a simplest method which can be started from racemic hydroperoxide and to be applicable to other racemic ones.

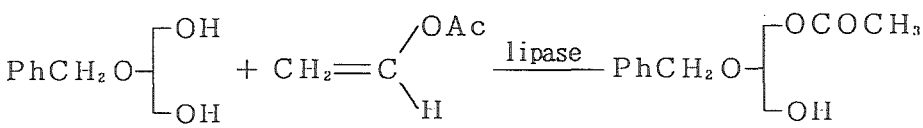
Optically active [1,1'-binaphthyl]-2,2'-diol (binaphthol) (48) has been used frequently as a chiral auxiliary in recent years because of its efficient stereochemical control element in asymmetric synthesis[29]. Preparation of the optically active binaphthol, however, rater time-consuming and more convenient method has been desired although it has been commercially supplied with good prices.




(46) (47) (48)

Kinetic resolution of racemic binaphthol was challenged by Oda et al. using *Pseudomonas fluorescens* lipase in organic medium. The monoacetylation of the racemic diol (46) was conducted with vinyl acetate in the presence of excess of the lipase at 40°C in a mixture of dry isopropyl ether and dry acetone. Thus, when the reaction was quenched at 52% conversion, the authors obtained monoacetate (47) having 95%e.e. and remained diol (48) with 89%e.e. One of the keys in this system is to use vinyl acetate which is an highly activated irreversible acetylation reagent. Thus, racemic binaphthol was also found to serve as an unnatural substrate and this method will be of much use for preparation of other optically active binaphthols[30].

As a final but important example should be cited here for enzymatic syntheses of optically active glycerides[31]. Achiwa et al. reported lipase-catalyzed enantiotopic group differentiation reaction of 2-O-alkyl-1,3-propanediol (49) affording optically active glyceride derivative (50)[32].

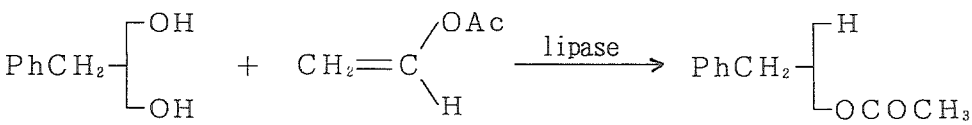



(49) (50)

*Pseudomonas fluorescens* lipase was applied to the substrate with excess of vinyl acetate and the author obtained the mono-ester (50) in 92% isolated chemical yield and 94%e.e. In this system, since no further acetylation of the product (50) occured and stereoselectivity was reasonably high, the general characteristic of enantiotopic group differentiation reaction was idealy realized and approximately all of the substrate was converted to the optically active product mono-acetate. In addition, excess of vinyl acetate was used as an acetylation reagent

and as an organic medium. Other acetylation reagents were also used with comparable results. This approach would be of considerable synthetic value particularly for optically pure phospholipid analogues including anti-cancer drugs, platelet activating factors, inhibitor of proteine kinase C and other physiologically important substances.

Achiwa et al. extended their works to the enantiotopic group differentiation of 2-alkyl-1, 3-propanediols by lipase-catalyzed mono-acylation via transesterification under non-aqeous condition[33]. Thus, when 2-benzyl-1, 3-propanediol (51) was submitted to the mono-acetylation by use of lipase P from *Pseudomonas fluorescens* or lipase B from *Pseudomonas fragi* in the presence of excess of vinyl acetate, (*R*)-2-benzyl-1, 3-propanediol mono-acetate (52) was obtained in 96% chemical yield with 97%e.e. and in 80% chemical yield with 77%e.e. respectively. This




(51) (52)

optically active alcohol was converted to (*S*)-3-isopropylsulfonyl-2-benzylpropionic acid, a key compound for synthesis of renin inhibitor. One of the most interesting points of this study is that mono-acetylation of 2-benzyl-propanediol afforded (*R*)-product whereas (*S*)-form was obtained from 2-O-benzyl-propanediol by the same enzymatic reaction. This outcome suggested that, so far as in the lipase-catalyzed mono-acetylation under nonaqueous condition, such small change of the substrate structure altered drastically the stereochemistry of the reaction product.

In summary, some asymmetric syntheses in recent years were presented briefly reviewing the strategies or methods from standpoints of stereochemical determining factor. The number of examples was rather limited emphasizing our own resuts. Nevertheless, some accounts described for each system should serve for further studies in addition to chemical intuitions as well as unique ideas of individual workers.

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## 不斉合成における最近の手法と考察(総説)

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不斉合成における立体選択性の向上に必要な条件について一般的に考察し，最近の研究から個々の例として，NADHモデル反応，相関移動触媒を用いる不斉エポキシ化反応，無水マロン酸の光学活性アルコキシドアニオンによるエナンチオトピックグループ選択的不斉加水分解反応，酸触媒分子内不斉ラクトン化反応，光学活性ルイス酸触媒を用いる不斉デイールズ-アルダー反応，不斉アルドール縮合反応，光学活性ホモアリルアルコール合成，リパーゼによるラセミヒドロペルオキシドとラセミビナフトールの速度論的光学分割及びメソ-2-O-ベンジル-1,3-プロパンジオールとメソ-2-アルキル-1,3-プロパンジオールの不斉モノアセチル化反応を紹介するとともに，その手法に対して若干の考察を行った.