Bull. Inst. Chem. Res., Kyoto Univ., Vol. 67, No. 3, 1989

Review

Asymmetric Reduction of Ketones with Microbes

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Received July 24, 1989

Progress in studies on asymmetric reduction of carbonyl compounds with microbes are described.

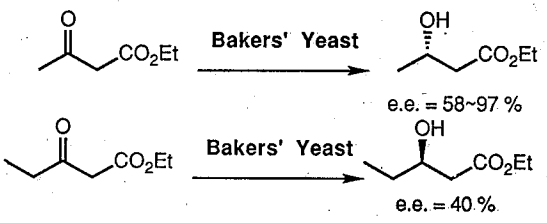
KEY WARDS: Reduction/ Asymmetric/ Microbe/ Keto ester/ Hydroxy ester/

The use of biocatalysts has become an important procedure in the field of asymmetric syntheses because the procedure introduces chiral centers into an organic molecules quite easily. In this article, we describe recent progress in asymmetric reduction mediated by microbes.

Reduction of Keto Esters

Keto esters are easily reduced by microbes while the stereoselectivity of the reduction is not always high. Oftenly, bakers' yeast is used for the reduction because it is a cheap and easily obtainable "reagent". Handling of bakers' yeast is easy even for organic chemists who are not familiar to microbes. Stereochemistry of the reduction is largely affected by a small difference in the structure of substrate. The reduction of ethyl 3-oxobutanoate with bakers' yeast, for example, gives the corresponding (*S*)-hydroxy ester in 58–97% e.e.[1] On the other hand, the yeast reduction of methyl 3-oxopentanoate gives the corresponding (*R*)-hydroxy ester in 40% e.e. (Scheme 1).[2] The reduction of alkyl 5-benzyloxy-3-oxopentanoate affords (*S*)-

Scheme 1



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5-(benzyloxy)-3-hydroxypentanoate in 96–30% e.e.[3] The reduction of ethyl 4-*t*-butoxy-3-oxobutanoate yields the corresponding (*S*)-3-hydroxy ester in 99% e.e. while the reduction of the 4-ethoxy derivative is not stereoselective.[4] The reduction of δ- or γ-keto acid with baker's yeast gives the corresponding (*R*)-hydroxy ester in high (98%) e.e.[5] The reduction of ethyl 2-(2-oxocyclohexyl)-2-oxoacetate gives a mixture of diastereomers of ethyl 2-(2-oxocyclohexyl)-2-hydroxyacetate, which is converted into (*R*)-hexahydromandelic acid with 99% e.e.[6]

Stereochemical Control in Microbial Reduction

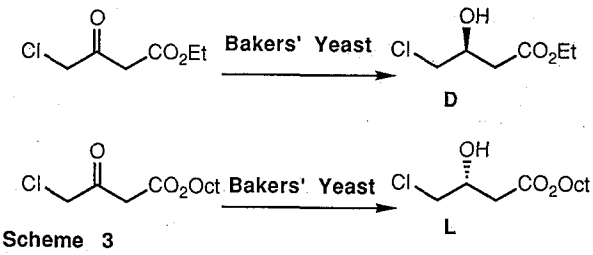
Since a microbial reduction usually affords an alcohol with unsatisfied e.e., a method to control the stereochemistry is required to employ the reduction for organic syntheses. In 1983, Sih *et al.* found that the reduction of ethyl 4-chloro-3-oxobutanoate with bakers' yeast gives the (D)-hydroxy ester in low e.e., whereas the reduction of the corresponding octyl ester yields the (L)-hydroxy ester in high e.e. (Scheme 2).[7] This method was applied to the preparation of (L)-3-hydroxypentanoate (Scheme 3), which was used further to the total synthesis of the pheromone of male swift mosh.[8] Hirama *et at.* reported that the reduction of ethyl 3-oxohept-6-enoate with baker's yeast gives the (D)-hydroxy ester in 80% e.e. while that of the corresponding acid yields the (D)-hydroxy acid in 99% e.e. (Scheme 4).[9] These two reports suggest that one can control the stereochemistry of the yeast reduction. To obtain an (L)-hydroxy ester, octyl ester is suitable and free acid is recommended to obtain a (D)-hydroxy acid.

Sih *et al.* isolated three enzymes that participate to the reduction of β-keto esters.[10] All of them employ NADPH as the coenzyme and one of them is the fatty acid synthetase (FAS) which reduces β-keto esters to yield β-hydroxy esters of D-configuration (D-enzyme). Others are D- and L-enzymes. Based on the kinetic measurement, it was found that k_{cat}/K_m of the FAS decreases as the ester group become larger, and K_m of the L-enzyme also decreases as the bulkiness of the ester group becomes larger. Then it was concluded that FAS is the main enzyme which reduces ethyl 4-chloro-3-oxobutanoate while the L-enzyme is the main enzyme which participates to the reduction of octyl 4-chloro-3-oxobutanoate (Scheme 5). The reduction of methyl 5-benzyloxy-3-oxopentanoate with bakers' yeast affords the (D)-alcohol in 33% e.e. When the benzyloxy group is substituted by a hydroxyl group and the methyl ester is converted into the pentyl ester, then the (L)-alcohol is obtained with as high e.e. as 87% (Scheme 6).[11] The corresponding octyl ester does not afford a good result. Methyl 5-benzoyloxy-3-oxopentanoate was also reduced with baker's yeast by another group of chemists to obtain the (L)-alcohol in 30% e.e.[3] They improved the e.e. up to 96% by using the corresponding pentyl or 2,2-dimethylpropyl ester. The difference in configuration of the product in these two reports might stem from a difference in bakers' yeast used for the reduction.

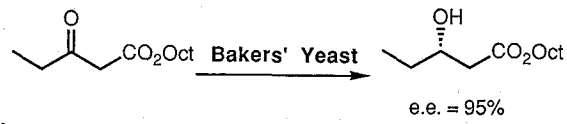
Stereochemical control by employing the immobilization technique was reported. The reduction of methyl 4-chloro-3-oxobutanoate with "free" bakers' yeast gives the corresponding (L)-hydroxy ester in 31% e.e., whereas that with polyurethane-im-

mobilized baker's yeast affords the (D)-hydroxy ester in 90% e.e. (Scheme 7).[12] In the reduction of α-keto esters, the use of hexane as a solvent shifts the stereochemistry of reduction toward the (D)-side. Thus, (L)-hydroxy esters are obtained from the reduction with "free" bakers' yeast in water while the corresponding (D)-hydroxy esters are obtained from the reduction in hexane with bakers' yeast immobilized by polyurethane (Scheme 8).[13] An inhibitor such as allyl alcohol or an α,β-unsaturated carbonyl compound shifts the stereochemistry of yeast reduction toward the (D)-side (Scheme 9).[14,15] Thus, (D)-3-hydroxy alkanoates were obtained in high e.e. from the reduction of β-keto esters with bakers' yeast treated by an inhibitor. To control the stereochemistry of yeast reduction toward the (L)-alcohols, the effect of added salt was studied. In the reduction of β-keto esters with bakers' yeast immobilized by magnesium arginate, (L)-hydroxy esters were obtained in high e.e.s (Scheme 10).[16] Substrate concentrations affects the stereochemistry of reduction. Thus, from yeast reduction of ethyl 3-oxobutanoate, ethyl (L)-3-hydroxybutanoate is obtained in 58% e.e. at the substrate concentration of 20 g/l whereas

Scheme 2

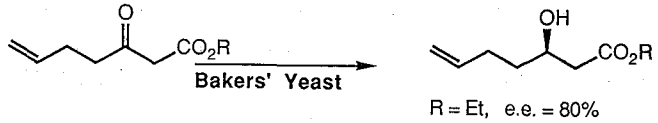


Scheme 3



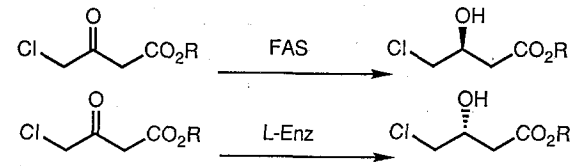
e.e. = 95%

Scheme 4



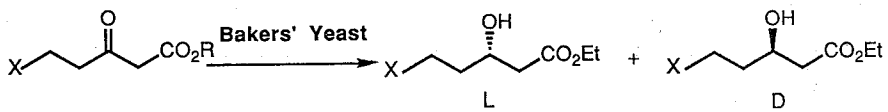
R = Et, e.e. = 80%
H, e.e. = 99%

Scheme 5



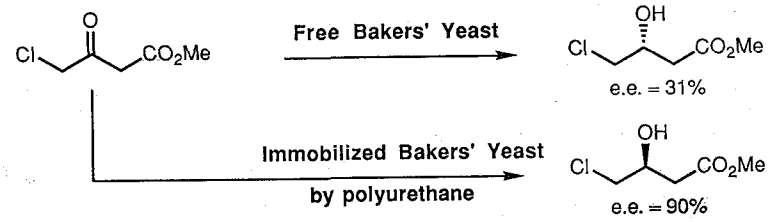
R = Et, FAS >> L-Enz
Oct, FAS << L-Enz

Scheme 6

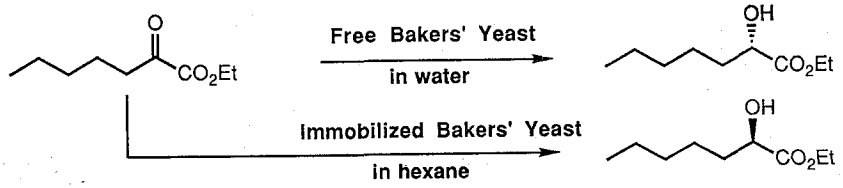


R = Me, X = OCH_2Ph	1	:	4.0
R = C_5H_{11}, X = OH	10.2	:	1

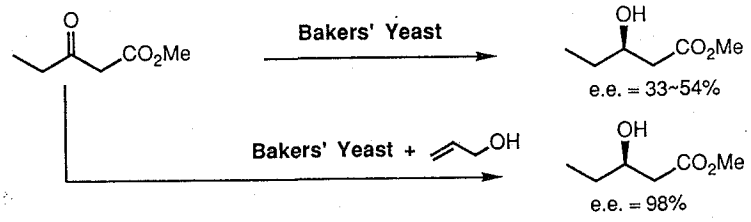
Scheme 7



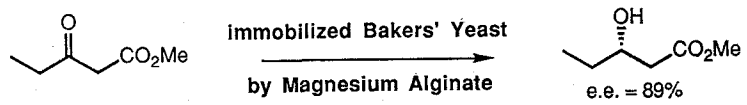
Scheme 8



Scheme 9



Scheme 10



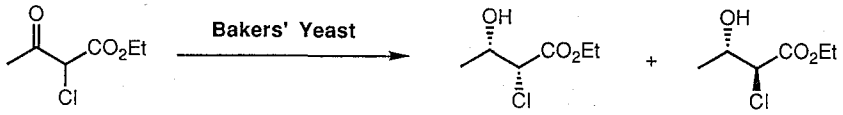
the e.e. increases to 94–97% at the concentration below 1 g/l.[1] The presence or absence of ethanol as well as its concentration affects the stereochemistry of reduction of ethyl 4-benzyloxy-3-oxobutanoate with bakers' yeast.[17] Although the 4-benzyloxy derivative does not exert high e.e., the 4-*t*-butyl derivative gives the (L)-hydroxy ester in high (97%) e.e.[4]

Diastereo-selective Reduction

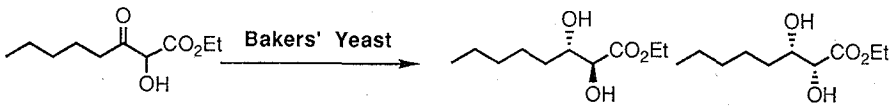
The reduction of 2-substituted 3-oxobutanoate usually yields a mixture of *syn*-

and *anti*-diastereomers. In fact, the reduction of 2-chloro- or 2-hydroxy-3-oxobutanoate affords a mixture of diastereomers. Thus, the reduction of ethyl 2-chloro-3-oxobutanoate with bakers' yeast gives a 1:1 mixture of *syn*- and *anti*-products in which the stereochemistry at the 3-position is *S* in both isomers (Scheme 11).[18] (−)-Oudemansin B was synthesized from this chiral building block. The reduction of ethyl 2-hydroxy-3-oxooctanoate with bakers' yeast yields a mixture of *syn*- and *anti*-diastereomers. These diastereomers were separated each other and found that

Scheme 11

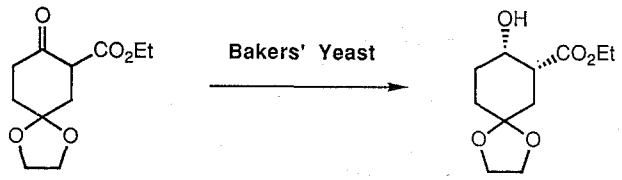


Scheme 12

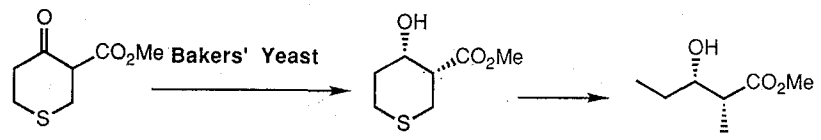


Scheme 13

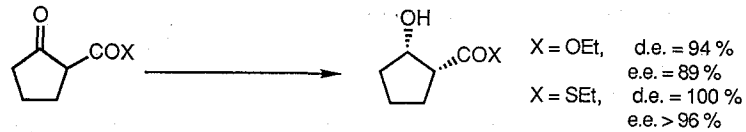
Scheme 14



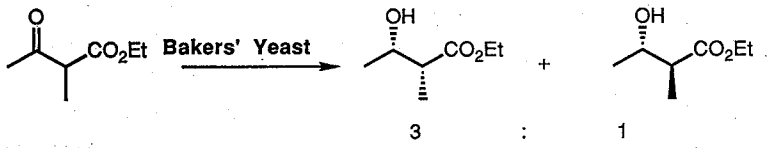
Scheme 15



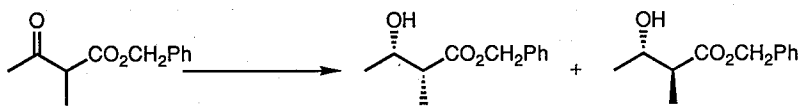
Scheme 16



Scheme 17



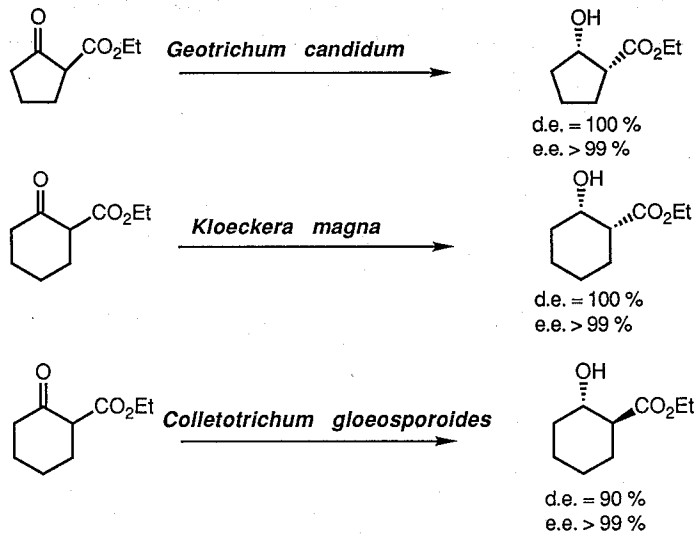
Scheme 18



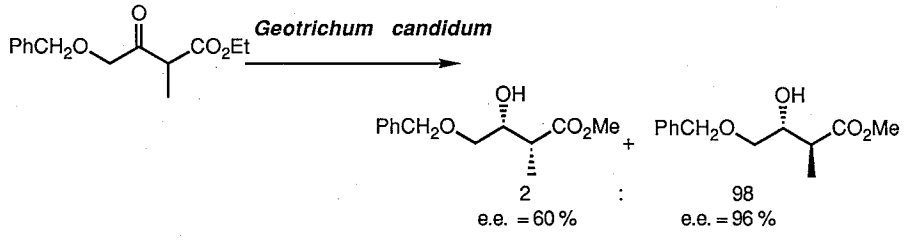
Bakers' Yeast 67 : 33
e.e. = 99 % e.e. = 84 %

Rhodotorula glutinis
94 : 6
e.e. = 97 % e.e. = 87 %

Scheme 19



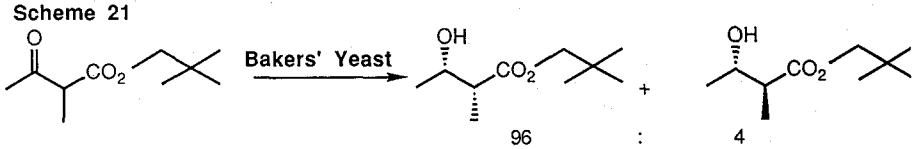
Scheme 20



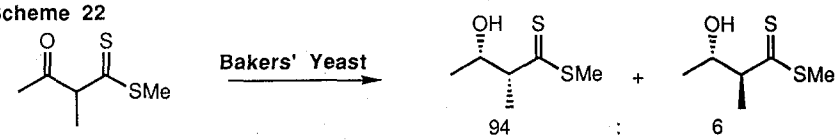
the e.e. of the *anti*-product is 97% while the e.e. of the *syn*-product is 70% (Scheme 12).[19] From the *anti*-product, a key intermediate of Pestalotin syntheis was prepared. The substrates mentioned above contain either chloro or oxygen substituent at the α-position and they are hardly enolizable. However, the substrate with an α-alkyl group enolizes easily and racemization between (2*S*)- and (2*R*)-isomers takes

place quite easily. Then, the reduction of a substrate of this class may proceed diasteroselectively if one of the two enantiomers, say the 2*S*-isomer, is reduced faster than the other, say the 2*R*-isomer, and the consumed substrate is supplied by racemization faster than the reduction. When the reduction at the 3-position proceeds enantioselectively, the reduction of this type is regarded as diastereoselective. The reductionof 2-ethoxycarbonylcyclohexanone gives the *cis*-(1*R*,2*S*)-hydroxy ester in 95% d.e. with 86% e.c. (Scheme 13).[20,21] To improve the e.e. and to prepare a new chiral building block, the 4,4-ethylenedioxy derivative of the above substrate was synthesized and was reduced with bakers' yeast and the *cis*-hydroxy ester was obtained as a sole product with the e.e. of 98.4% (Scheme 14).[22] Yeast reduction of methyl tetrahydro-4-oxo-2H-thiopyran-3-carboxylate gives the corresponding hydroxy ester in 98% d.e. The product was desulfurized to give methyl (2*R*,3*S*)-2-methyl-3-hydroxy pentanoate. The d.e. was excellnet in this case, however, e.e. was not satisfactory (85%) (Scheme 15).[23,24] Anhydroserricornin was synthesized from the product. Another method to improve the e.e. of 2-alkoxycarbonylcyclopentanone was tested by modifying the ester to the corresponding thiolester. Thus, only

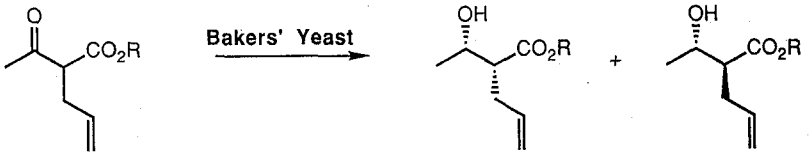
Scheme 21



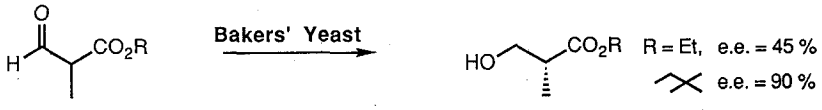
Scheme 22



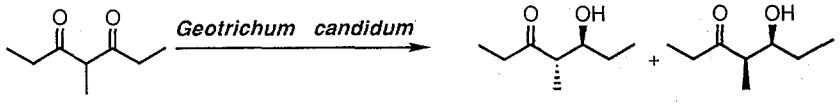
Scheme 23



Scheme 24



Scheme 25



the *cis*-isomer was obtained in>96% e.e. (Scheme 16).[25]

The yeast reduction of acyclic 2-alkyl-3-oxoalkanoate usually gives lower d.e. than the cyclic derivatives. The reduction of ethyl 2-methyl-3-oxobutanoate yields a mixture of 3-hydroxy products in which the *syn*:*anti* ratio is 3:1 (Scheme 17).[26] The reduction of the corresponding benzyl ester also results in low d.e. which can be improved by the reduction with other microbe (Scheme 18).[27] Several microbes were tested to reduce esters of cyclopenta- or cyclohexanone-2-carboxylic acid. The reduction of 2-ethoxycarbonyl-cyclopentanone with *Geotrichum candidum* gives the *cis*-(1*S*,2*R*)-hydroxy ester exclusively. However the microbe that reduces the same substrate to the corresponding *trans*-isomer selectively can not be found. The reduction of the corresponding cyclohexanone derivative with *Kloeckera magna* gives the *trans*-(1*S*,2*S*)-hydroxy ester at the ratio of *trans*:*cis*=95:5 (Scheme 19).[28] Screening of microbes for the reduction of esters of 4-benzyloxy-2-methyl-3-oxobutanoic acid was investigated and the microbe that reduces the substrate to the *anti*-product was found. However, no microbe was appointed to the catalyst which gives the *syn*-product exclusively. Thus, the reduction of methyl 4-benzyloxy-3-oxo-2-methylbutanoate with *Geotrichum candidum* gave the *anti*-product in 96% e.e. (Scheme 20).[29]

Diastereoselectivity of the reduction of acyclic 2-alkyl-3-oxobutanoates was investigated by modifying the ester moiety to the octyl or 3,3-dimethylpropyl group. Thus, the *syn*-product was obtained in high d.e. in the reduction of 3,3-dimethylpropyl 2-methyl-3-oxobutanoate (*syn*:*anti*=96:4) (Scheme 21).[30,31] The diastereoselectivity can also be improved by using dithioester derivatives. Thus, methyl 2-methyl-3-oxodithiobutanoate gives the *syn*-hydroxy ester in high d.e. (*syn*:*anti*=94:6) (Scheme 22).[32]

Yeast reduction of 2-methyl-3-oxobutanoate mainly affords the *syn*-product while that of the 2-allyl derivative yields the *anti*-product, although the diastereoselectivity is low in the latter reduction.[26] Modification of the ethyl ester to the corresponding *t*-butyl ester increases the *anti*-selectivity; (2*S*,3*S*)-hydroxy ester was obtained in high d.e. (*syn*:*anti*=6:94) (Scheme 23).[31] The reduction of 2-methyl-3-oxopropionate yields a primary alcohol where the 3-position is not chiral but the chirality is introduced in the 2-position by the same reason described for the reduction of 2-alkyl-3-oxobutanoate. That is, instead of a diastereomer, an enantiomer is obtained by this reduction. The reduction of 2-methyl-3-oxopropionate has been reported by Seebach, in which the (*R*)-hydroxy ester is obtained with unsatisfied e.e.[33] Stereochemical control of this reduction was achieved by modifying the substrate to the 3,3-dimethylpropyl ester, which gives the (*R*)-hydroxy ester in 90% e.e. (Scheme 24).[34]

Reduction of a β-diketone which has a substituent at the α-position gives a mixture of diastereomers. Yeast reduction of 3-methyl-2,4-pentanedione yields mainly the *syn*-hydroxy ketone, although diastereoselectivity is not high (*syn*:*anti*=4:1).[35] The effect of oxygen atmosphere on the reduction of 2-methyl-heptan-3,5-dione with resting cells of *Geotrichum candidum* was reported. The reduction under aerobic conditions gave mainly the *anti*-product whereas the *syn*-product was obtained mainly under anaerobic conditions (Scheme 25).[36] The authers proposed that under an-

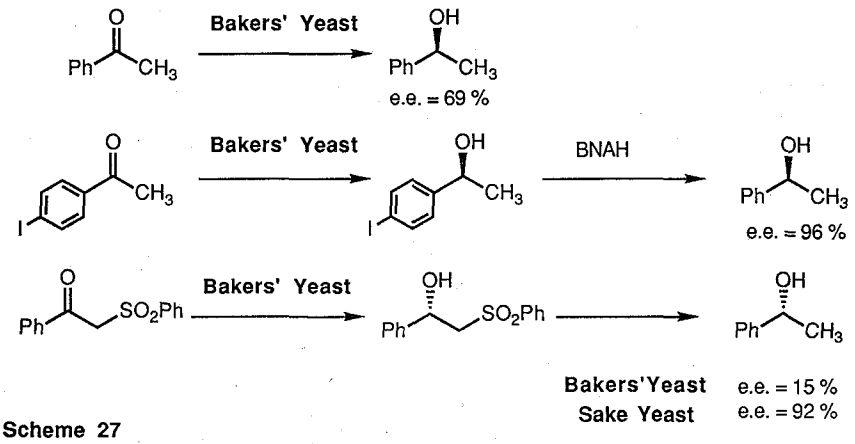
aerobic conditions, many dehydrogenases of the oxidative methabolism and the enzymes that cause further degradation of the product are inhibited.

Reduction of Hetero Atom-Containing Ketones with Microbes

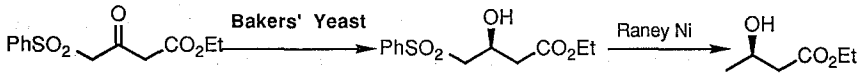
Since hetero atoms are usually converted into other functional groups without difficulty, the reduction of hetero atom-substituted ketones with microbes may afford useful chiral synthons in organic syntheses. The advantage of using a hetero atom-substituent is that the reduction may be affected by the substitution and improvement of the selectivity of the reduction is expected.

Acetophenone is reduced with bakers' yeast to give the (*S*)-alcohol in low e.e. (69%).— To improve the selectivity, iodine was introduced at the *para*-position of the phenyl ring of acetophenone and the resulted *p*-iodoacetophenone was reduced with bakers' yeast. Surely, the e.e. of the product increased to 96%.[38] Iodine

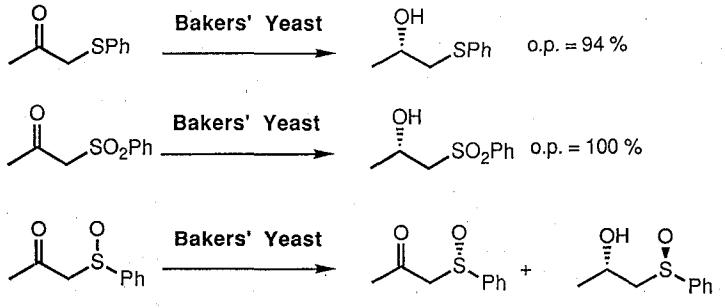
Scheme 26



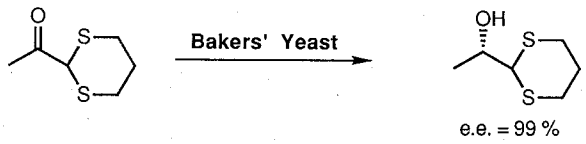
Scheme 27



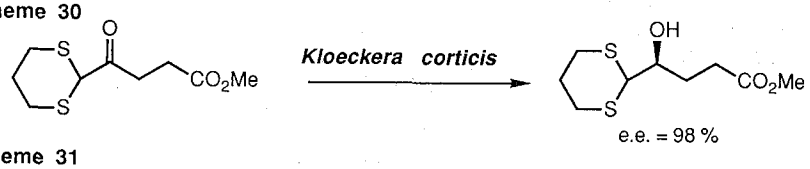
Scheme 28



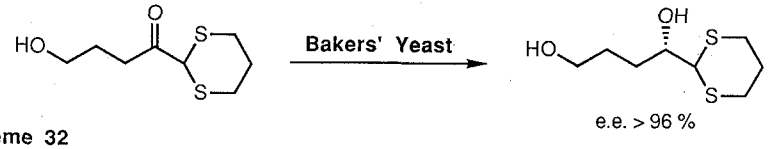
Scheme 29



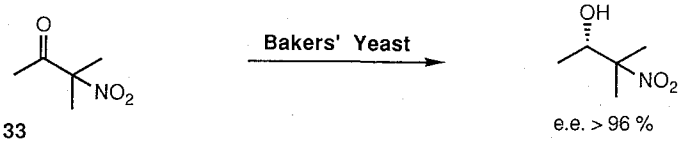
Scheme 30



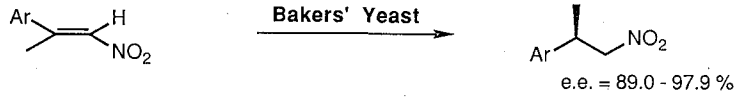
Scheme 31



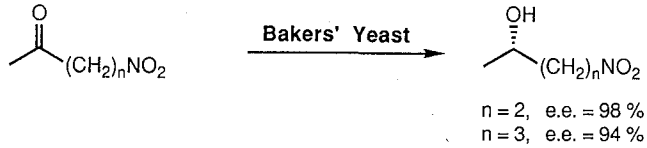
Scheme 32



Scheme 33



Scheme 34



was removed by the reduction with an NADH model to give (*S*)-2-phenylethanol in 96% e.e. (Scheme 26). The other enantiomer, (*R*)-alcohol, was obtained by modifying the substrate with a phenylsulfonyl group. Thus, phenylsulfonylacetophenone was reduced with bakers' yeast to give the (*S*)-alcohol which was converted into (*R*)-2-phenylethanol. Although the selectivity in the reduction with bakers' yeast was not good (15%), the use of Sake yeast improved the e.e. as high as 92%. The product was desulfurized with Raney nickel W-4 to afford (*R*)-2-phenylethanol in 92% e.e.[38] A dramatic effect of phenylsulfonyl group on stereochemistry of the reduction was shown in the reduction of a β-keto ester. Although yeast reduction of ethyl 3-oxobutanoate gives the (L)-carbinol, substitution of a phenylsulfonyl group at the 4-position turned the stereochemistry of the reduction toward the (D)-side. Thus, the (D)-hydroxy ester was obtained in high e.e. (Scheme 27).[38]

To study the effect of sulfur-containing functional group on yeast reduction, three acetone derivatives ($CH_3COCH_2S(O)_nPh$, n=0, 1, 2) were reduced with bakers' yeast (Scheme 28).[39] The (*S*)-alcohols are obtained in every cases. The

sulfenyl ketone affords the product in low chemical yield with 94% optical yield, whereas the reduction of the sulfonyl ketone gives the product in a high chemical yield with 100% optical yield. The reduction of the (±)-sulfinyl ketone, on the other hand, remained the $(S)_S$-isomer of the starting material unreacted and afforded optically pure (S_C, R_S)-sulfinyl alcohol. This optical resolution was applied to the synthesis of Diaparlure, a pheromone of gypsy moth.[40]

Introduction of a 1,3-dithiane group into ketones is a useful method to improve the stereoselectivity of the reduction. Yeast reduction of 1,3-dithian-2-yl-propan-2-one gives the corresponding (*S*)-alcohol with more than 99% e.e. (Scheme 29).[41] The chiral alcohol was used for the synthesis of (*S*,*S*)-(+)-Grahemimycin A_1. Reduction of the 6-(1,3-dithiane) derivative of methyl 5,6-dioxohexanoate was tested to prepare a chiral synthon for the synthesis of an intermediate to the arachidonic acid cascade. Although the carbinol of (*R*)-configuration was required, the (*S*)-carbinol was obtained in high e.e. by the reduction with *Kloeckera corticis* (Scheme 30).[42] The reduction with other microbes are not stereoselective. Yeast reduction of 1-(1,3-dithian-2-yl)-5-hydroxy-2-pentanone gave the corresponding optically pure (*S*)-carbinol (Scheme 31),[43] which was converted into a natural product obtained from strains of *Streptomyces*.

Nitro group is known to construct useful building blocks because it has a facility to stabilize an α-carbanion, then to promote the formation of a new carbon-carbon bond. Yeast reduction of 3-methyl-3-nitro-2-butanone yields the corresponding nitro alcohol with high e.e. (Scheme 32).[44] Nitro olefins were reduced with bakers' yeast to the corresponding saturated nitro compounds. The specificities are 89.0–97.9% e.e. (Scheme 33).[45] Ketones with a β- or γ-nitro group were reduced with bakers' yeast to give the corresponding nitro alcohols with high e.e. (Scheme 34).[46]

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