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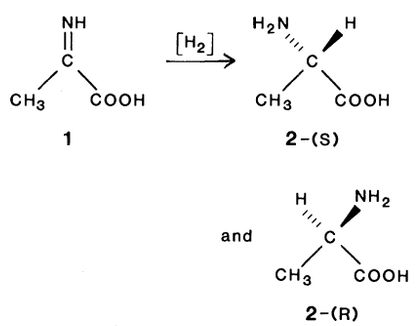
Current Status of Asymmetric Synthesis

Harry S. Mosher and James D. Morrison

Summary. In the last 30 years the subject of asymmetric synthesis has grown from a little studied academic niche in organic chemistry to an intensely investigated field of commercial importance and heightened general interest. Impressive advances have been made in several areas, notably catalytic asymmetric homogeneous hydrogenation, catalytic asymmetric epoxidation of allyl alcohols and stereochemical control of carbon-carbon bond-forming reactions. Asymmetric synthesis must now be deliberately considered along with other available methods as a practical strategy for the synthesis of any chiral compound.

The organic constituents of plants, animals, and microorganisms—from the most primitive to the most highly developed—are composed of molecules that are chiral (*1*). Life processes on a molecular scale take place between chiral molecules in a chiral environment; presumably, this has been so since primordial biotic times (*2*). How did the selection (or production) of one enantiomer of a chiral pair of molecules take place in a prebiotic world where presumably ordinary chemical processes had no statistical preference for selecting (or producing) one isomer over the other? For example, if an achiral (*1*) amino acid precursor **1** is reduced in a symmetrical environment with a symmetrical reagent (an achiral reaction), a 50:50 mixture of the two enantiomeric (*3*) forms, **2**-(*S*) and **2**-(*R*) of the amino acid, results. The stereochemical situation is depicted in Fig. 1. The right and left faces of symmetrical structure **1** (Fig. 1) are indistinguishable to a symmetrical reagent such as hydrogen; therefore, attack upon either face is equally probable. Presumably this was the situation in prebiotic times before chiral molecules existed on earth (*2*). However, these faces are not the same to a chiral reagent such as an enzyme. When structure **1** is viewed from the vantage point of the H_2 on the left, the NH, COOH, and CH_3 groups are arranged in a clockwise sequence; however, when viewed from the vantage point of the H_2 on the right, the same three groups occur in a counterclockwise sequence. These are designated prochiral faces. A chiral reagent attacking the prochiral faces of this symmetrical substrate can recognize the difference, thereby giving rise to unequal amounts of the products from the two modes of attack. The difference may vary from essentially zero to 100 percent; for instance, if 45 percent of **2**-(*R*) and 55 percent of **2**-(*S*) are formed, then there is a 10 percent excess of the **2**-(*S*) enantiomer, namely, a 10 percent enantiomeric excess. In the reduction of such a substrate by an enzyme system, the perfect chiral reagent, one side will be attacked to the virtual exclusion of the other, leading to a 100 percent enantiomeric excess. Natural processes have resulted in the evolution of enzymes that for the most part produce only the amino acids corresponding to the **2**-(*S*) configuration.



Because of the predominance of chiral organic molecules in nature, we must develop the best ways of obtaining these compounds so that their properties and reactions can be studied, and so that structural and stereochemical variations that do not occur in nature can be prepared. Chiral substances may be obtained in many ways (*4*): they may be isolated from a plant, animal, or microbial source; synthesized from a chiral substance isolated from nature; or obtained from a racemic mixture by use of a chiral resolving agent to accomplish the separation. In this article, we discuss the process of asymmetric synthesis, whereby an achiral starting material is converted into a chiral product by a reaction involving a chiral reagent.

Before 1965, asymmetric synthesis was generally considered a rather esoteric subject; recently it has undergone an exponential growth as reflected by publications and patents. In the 5-year period 1971 to 1976, *Chemical Abstracts* listed 47 entries under "Asymmetric synthesis." In the 5-year period, 1976 to 1981, there were more than 940 such entries (*5*). This is more than the total number of references found in the monograph on asymmetric synthesis (*4*) covering the literature from the turn of the century to 1970.

We believe that few recent basic breakthroughs have been made in the principles governing the stereochemistry of asymmetric synthesis. These principles were present in an embryonic form in the early 1950's with the contributions of Barton (*6*), Doering (*7*), Mosher (*8*), Cram (*9*), Prelog (*10*), and others. However, spectacular progress has been made in the application of stereochemical principles to organic synthesis. The most innovative advancements have been in the applications of metallo-or-

Harry S. Mosher is professor emeritus, Department of Chemistry, Stanford University, Stanford, California 94305, and James D. Morrison is professor, Department of Chemistry, University of New Hampshire, Durham 03824.

ganic chemistry in which the central metal atom, along with a coordinated chiral ligand or ligands, is used to guide and closely orient the stereochemical course of the reaction (*11–15*). Examples of such reactions are the homogeneous hydrogenations catalyzed by rhodium-chiral phosphine (*11–15*), the chirally modified lithium aluminum hydride reductions (*16*); the peroxidic allyl alcohol oxidations catalyzed by titanium alkoxide and diethyl tartrate (*17*); and alkylations with organometal derivatives of internally coordinated chiral reagents such as oxazolines (*18*), oxathianes (*19, 20*), or chiral proline derivatives (*21*). Asymmetric synthesis must now be considered on an equal basis with other available methods as a practical approach for obtaining any specified chiral compound.

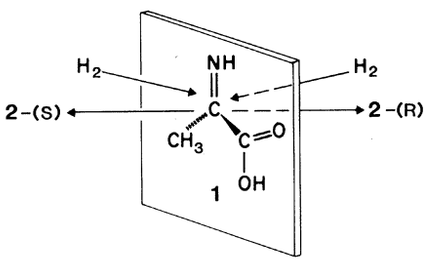
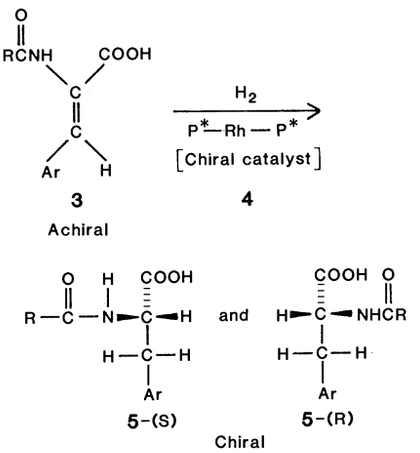


Fig. 1. Idealized model for attack of the reagent (H_2) on the prochiral faces of the carbon-nitrogen double bond in substrate **1**.

The subject of asymmetric synthesis has been extensively reviewed (*4, 22–28*). Therefore, we present in this article a limited number of examples that have been chosen because they represent an optimistic assessment of the current status of asymmetric synthesis. Many of these examples came from papers presented at the United States–Japan joint conference on asymmetric reactions and processes, held at Stanford University in the summer of 1981 (*27*). Our objective is to point out how recent developments have influenced the perspective of organic chemists with respect to the use of asymmetric synthesis of the preparation of chiral compounds.

Asymmetric Homogeneous Hydrogenations

Soluble cationic rhodium complexes of chiral tertiary phosphines (RR′R″P* symbolized by P*) catalyze asymmetric hydrogenations of unsaturated substrates. Such hydrogenations of α-acylaminoacrylic acids (**3**) in suitable cases have produced amino acid derivatives (**5**) approaching 100 percent enantiomeric purity.



More than a decade ago, germinal papers by Knowles and Sabacky (*29*) and Horner *et al.* (*30*) on phosphorus ligands chiral at phosphorus, and later by Morrison *et al.* (*31*) and Kagan and Dang (*32*) on phosphorus ligands chiral at carbon, triggered an explosion of interest in the potential of such systems (*11–15*). Vineyard *et al.* (*33*) at Monsanto Chemical Company developed a commercial synthesis of L-dopa (L-3,4-dihydroxyphenylalanine, **7**, a compound used in the treatment of Parkinson's disease), using hydrogenation by a rhodium catalyst incorporating the chiral diphosphine ligand (*R,R*)-DIPAMP (**8**). This industrially

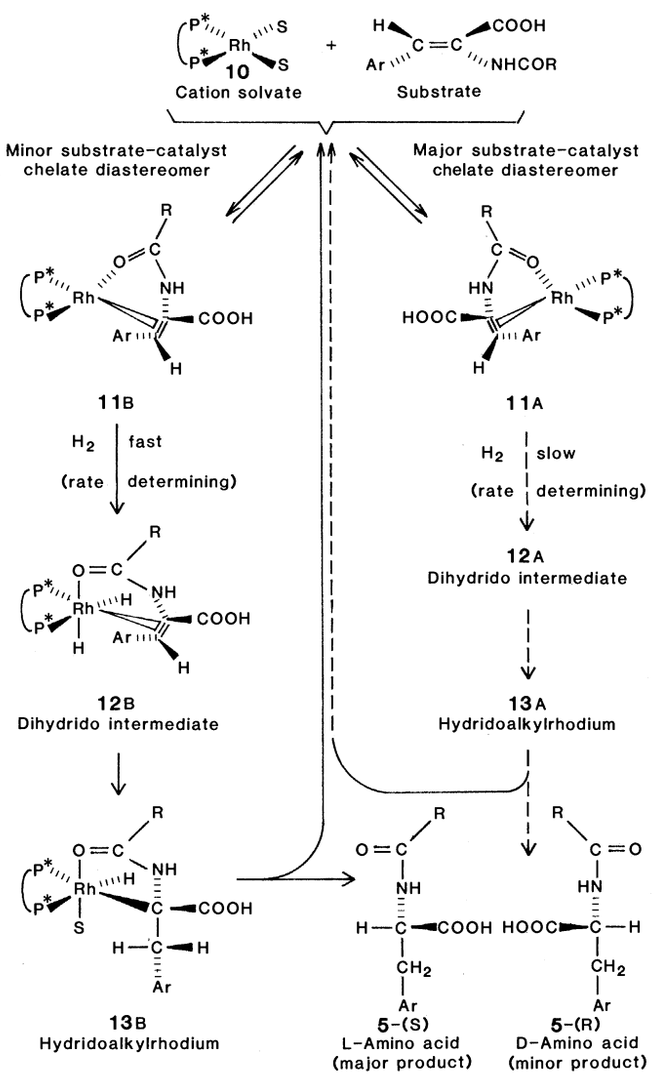
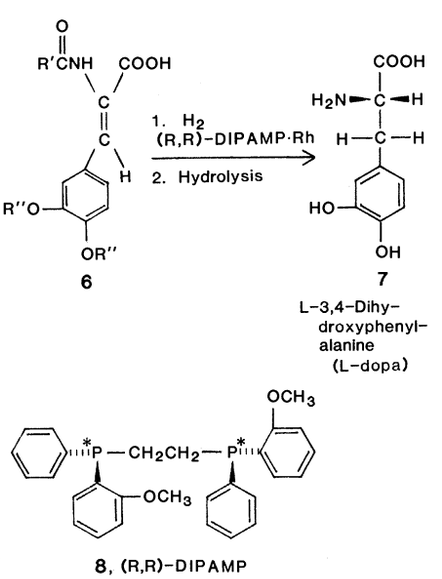


Fig. 2. Mechanism for asymmetric homogeneous hydrogenation with the rhodium chiral diphosphine ligand DIPAMP (**8**) represented by P*—P*. The solvent is designated *S*; *Ar* stands for an aryl group such as phenyl. Model according to Halpern (*12*).



successful application of asymmetric homogeneous hydrogenation—and others that can be imagined—stimulated a vast amount of activity in this area (*14*). More than 100 chiral phosphine ligands have been tested with various substrates; several such ligands are now commercially available. A large amount of a chiral product can be made from an achiral substrate by investing only a small amount of an active chiral catalyst. Even though the catalyst is relatively expensive, great economic leverage can be derived in suitable processes. This system is being used commercially to produce isotopically labeled amino acids. It is especially attractive for the preparation of rare D-amino acids and other chiral compounds for which alternative biochemical methods may not be suitable.

How does a diphosphine ligand such as **8** achieve this remarkable stereoselectivity? The currently accepted mechanism, represented in Fig. 2, has been deduced from kinetic, stereochemical, and x-ray structural evidence (*12*). Two diastereomeric catalyst-substrate chelates, **11A** and **11B**, are formed. The major chelate, observed in solution by nuclear magnetic resonance (NMR) is **11A**, from which the D-amino acid **5**-(*R*) should result. However, the major product is the L-amino acid **5**-(*S*). The minor diastereomeric complex, **11B**, which is in equilibrium with the major diastereomer, **11A**, and which is present in too small an amount to be observed by NMR, ultimately leads to the L-amino acid derivative **5**-(*S*). This happens because the subsequent rate-determining hydrogenation step shown in the reaction pathway on the left in Fig. 2 is much faster for the minor (**11B**) than for the major (**11A**) complex. After the initial equilibrium, the reaction path to the major product (Fig. 2) includes (i) the rate-determining addition of hydrogen to give the dihydrorhodium complex **12B**, (ii) the transfer of one hydrogen to carbon with formation of the chiral carbon-rhodium bond to give the hydridoalkyl rhodium intermediate **13B**, and (iii) the final irreversible transfer of hydrogen to carbon with retention of configuration to give the L-amino acid derivative, **5**-(*S*). The enantiomeric **5**-(*R*) product is formed to a small extent by a much slower reaction from the major complex **11A** by the pathway shown on the right in Fig. 2. The high stereoselectivity occurs because of the differences in steric fits, and therefore energies of activations, between the competing, rate-determining, diastereomeric transition states. The central rhodium atom organizes the reactants, chiral ligands, and solvent in a closely packed, sterically demanding array in intermediate **12**, which determines the chiral discrimination of the asymmetric reduction. Higher H_2 pressures may reduce the stereoselectivity by changing the relative concentrations of intermediate **12** and its diastereomer (*15*). The mechanistic details for chiral catalysts with monophosphine ligands versus diphosphine ligands may not be the same (*13*).

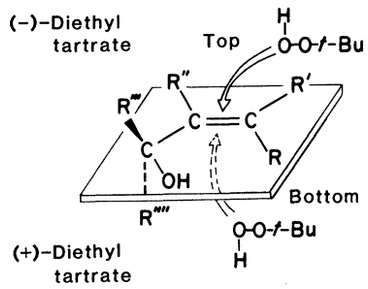
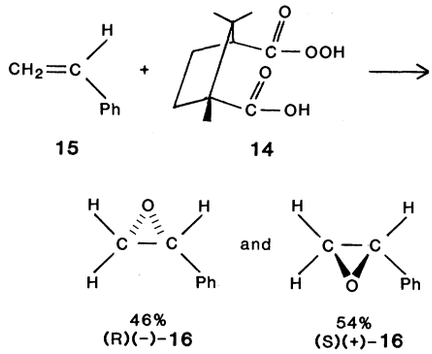


Fig. 3. Stereochemical model for Sharpless asymmetric epoxidation reaction (t-*BuOOH*, *tert*-butyl hydroperoxide).

The chiral phosphine-rhodium asymmetric hydrogenation systems represent a triumph of both synthetic and mechanistic chemistry. In ideal cases, it produces chiral products with enzyme-like efficiency.

Asymmetric Epoxidation

The counterpart to asymmetric hydrogenation is asymmetric epoxidation. Henbest (*34*) in 1965 pioneered the use of chiral monoperoxycamphoric acid (**14**) to produce chiral epoxides but with an asymmetric bias of 5 percent or less; Pirkle and Rinaldi (*35*) in 1977 described improvements that gave asymmetric epoxidations up to 9 percent enantiomeric excess. The following equations illustrate this reaction for conversion of styrene (**15**) to styrene oxide (**16**) with an 8 percent excess of the (*S*)-(+) isomer. Presumably the low stereoselectivity results from too great a distance between



the chiral-inducing centers and the peroxidic bond so that there is little steric discrimination during attack on one prochiral face of the olefin versus the other.

Asymmetric epoxidations with hydrogen peroxide and *tert*-butyl hydroperoxide catalyzed by chiral phase-transfer agents such as benzyl quinidinium salts, were studied by Wynberg and others (*36*) and found to be moderately successful. Sharpless and his students, using vanadium complexes (*37*), and Yamada *et al.* (*38*) using molybdenum complexes, independently reported the first metal-catalyzed asymmetric epoxidations. Additional examples were reported by Otsuka and his students (*39*) who, for example, described the treatment of squalene with a mixture of *tert*-butyl hydroperoxide, molybdenum oxide chelate, and the chiral inducing agent (+)-diisopropyl tartrate. This resulted in a high chemical yield of biogenetically important (*S*)-2,3-squalene epoxide in 14 percent enantiomeric excess. Studies on allylic alcohols were pursued by Sharpless and his students (*40–43*), who ultimately devised successful epoxidation, based on both organic and inorganic stereochemistry, which has given impressive results. In the Sharpless reaction, an allylic alcohol (**17**) is treated with a mixture of commercially available titanium tetra-isopropox-

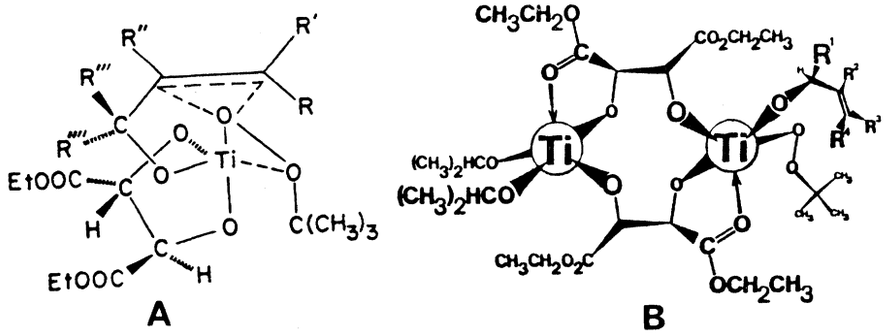
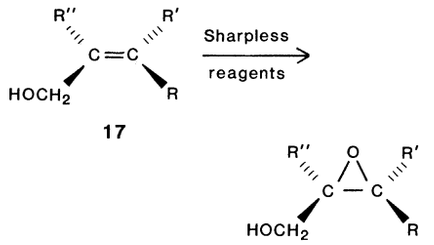
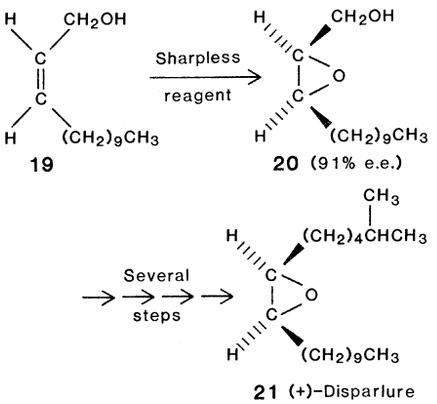


Fig. 4. Postulated organization of substrate (allylic alcohol), epoxidizing agent (*tert*-butyl hydroperoxide), chiral-inducing agent [(*R*,*R*)-(+)-diethyl tartrate], and titanium in the Sharpless reagent; (A) monomer model (*42*); (B) dimer model (*43*).

ide, *tert*-butyl hydroperoxide, and (+)- or (−)-diethyl tartrate to give an epoxy carbinol (**18**) in high chemical yield. So far, most reactions have given more than



90 percent enantiomeric excess, with many giving better than 95 percent enantiomeric excess. An equivalent amount of the titanium-tartrate reagent is used when the allylic alcohol has one or two substituents on the double bond, but tri- and tetra-substituted derivatives are so reactive that only a catalytic amount of the reagent is necessary. This catalytic asymmetric epoxidation is under intensive study as a practical method of introducing chirality into the intermediates for the synthesis of various commercially important biologically active compounds such as antibiotics, drugs, and insect pheromones (*44*). The following synthesis of the gypsy moth pheromone (+)-disparlure (**21**), starting with the achiral allylic alcohol **19**, illustrates one of its commercial applications.



The Sharpless allylic epoxidation catalyst begins to approach the stereoselectivity of an enzyme system and surpasses most enzymes in the variety of substrates it will accept. How does it work? It is clear that the titanium metal serves to bind and organize the epoxidizing agent (*tert*-butyl hydroperoxide), the chiral-inducing agent (diethyl tartrate), and the substrate (an allylic alcohol) in such a way that one face of the allylic alcohol is greatly favored over the other. Sharpless has proposed an empirical model to correlate the observed stereochemical results. Regardless of the nature of the substituents, when (*S*,*S*)-(−)-diethyl tartrate is used as the inducing agent, the oxygen of the epoxidizing agent is inserted onto the top face of the double bond for the orientation shown in Fig. 3. The use of natural enantiomeric (*R*,*R*)-(+)-diethyl tartrate results in preferential attack from the opposite side, with formation of the epoxide with reversed stereochemistry. A theoretical model of the transition state for this epoxidation was provisionally proposed (*42*) (Fig. 4A). The reagent is now considered to be a dimer (*43*); a transition state model incorporating this dimer structure is shown in Fig. 4B. Both models depict bonding of the allylic oxygen to a central titanium atom that organizes the epoxidizing agent (*tert*-butyl hydroperoxide), the chiral-inducing agent [(*R*,*R*)-(+)-diethyl tartrate], and the substrate into a compact structure that favors attack on the bottom face of the allylic double bond. The use of enantiomeric (*S*,*S*)-(−)-diethyl tartrate changes the combined electronic and steric effects so that attack on the opposite side of the allylic bond is favored, with formation of the enantiomeric product.

This may be the most innovative reaction introduced into organic chemistry in modern times. Masamune and Sharpless have collaborated to synthesize the four D-pentoses with this basic reaction followed by stereo-controlled opening of the epoxide ring (*41*). All eight isomeric L-hexoses (*43*) were then synthesized within a few months, an accomplishment that by older methods might take years.

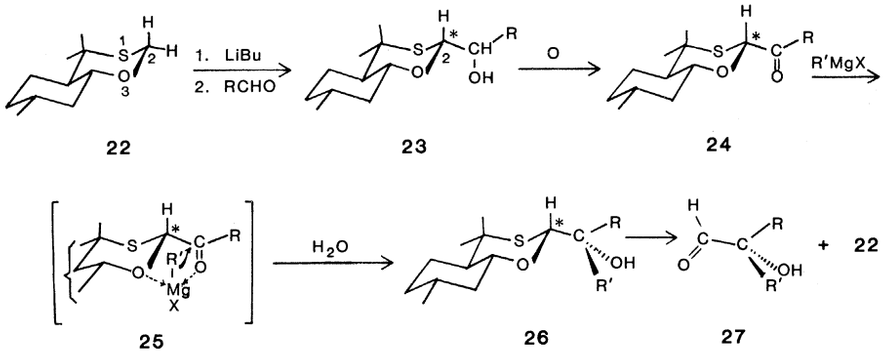


Fig. 5. A series of α-hydroxy aldehydes has been made by the Eliel oxathiane asymmetric synthesis (*19*, *20*, *27*) with enantiomeric purities of 90 to 98 percent.

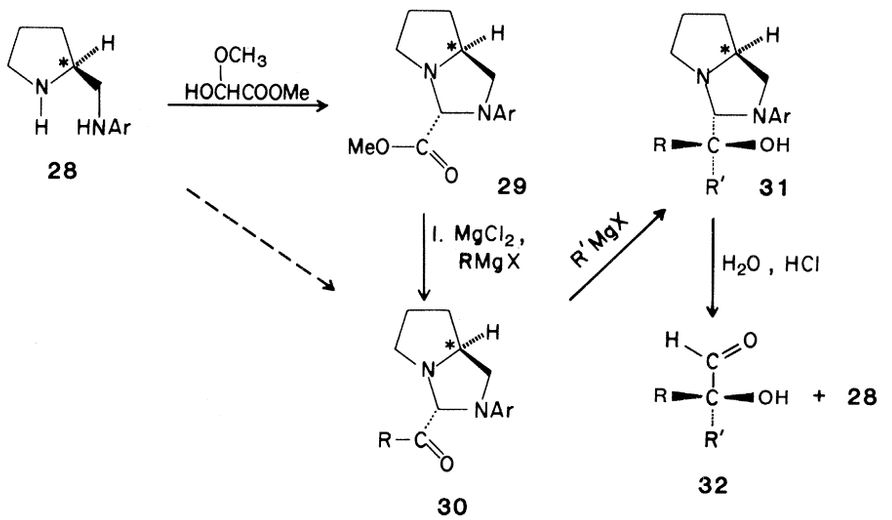


Fig. 6. The Mukaiyama chiral diamine asymmetric synthesis. By introducing the R and R′ groups in the opposite sequence, the enantiomeric α-hydroxy aldehyde **32** will be formed.

Chelation-Controlled Addition Reactions

Recent efficient asymmetric addition reactions have produced various types of chiral carbinols, α-hydroxy carbonyl compounds, acids, hydroxy acids, and their derivatives, all of which have become important in the construction of complex chiral molecules. These asymmetric syntheses have been constructed upon the solid foundation of knowledge accumulated and correlated by Cram beginning in 1952 (*9*) and expanded upon by others during the intervening years. These earlier results have been reviewed (*4*) and are summarized by what are

known as Cram's rules. The stereoselectivity of these addition reactions is greatly increased when there is a functional group, such as methoxy, to which the organometallic reagent can chelate. Chelation freezes out free rotation and increases rigidity, thereby accentuating and localizing steric effects. Recent application and expansion of this principle has led to several important, highly stereoselective, asymmetric syntheses.

Oxathiane system. In the system developed by Eliel (*19, 20*) (Fig. 5) a chiral oxathiane, **22**, which is prepared in three steps from the readily available natural (+)-pulegone, is converted to the anion that undergoes electrophilic substitution at C-2 when treated with an aldehyde to give the product **23**. Essentially a single configuration at C-2 is produced because the anion assumes an equatorial orientation for stereoelectronic reasons. Mixed configurations are formed at the adjacent secondary carbinol center of the product; however, oxidation in the next step to **24** destroys the chirality at this center. Because the chelation of magnesium is much greater to oxygen than to sulfur, as shown in **25**, the R′ group of the Grignard reagent preferentially attacks the front face of the carbonyl group on the side of the ring oxygen. Therefore, the diastereomer produced in 90 to 98 percent enantiomeric excess has the configuration shown in **26**. Treatment with thiocyanate and silver ions regenerates a precursor to the chiral-inducing pulegone derivative **22** and liberates the chiral hydroxy aldehyde **27** with an enantiomeric purity the same as that of the diastereomeric precursor **26**. Since the order of introducing R and R′ can be reversed, either enantiomer may be synthesized at will. The hydroxy aldehyde can either be oxidized to the corresponding chiral acid or reduced to the corresponding chiral glycol. Since there is an almost unlimited choice of R and R′ groups, this asymmetric synthesis is one of wide-ranging potential application. An example of such an application is the synthesis of (*R*)-mevalactone (*20*).

Aminal system. Mukaiyama's chiral aminal system (*21*) (Fig. 6) bears a certain resemblance to the oxathiane synthesis, but with nitrogen replacing oxygen and sulfur in the ring. The chiral diamine **28**, which is available from L-proline in three steps, can be converted into aminals **29** and **30**. Steric hindrance (rather than stereoelectronic control, as in the oxathiane system) directs the substituent at C-2 so that one enantiomer is formed to the virtual exclusion of the other. Treatment of **29** with a suitable Grignard reagent and **30** with another

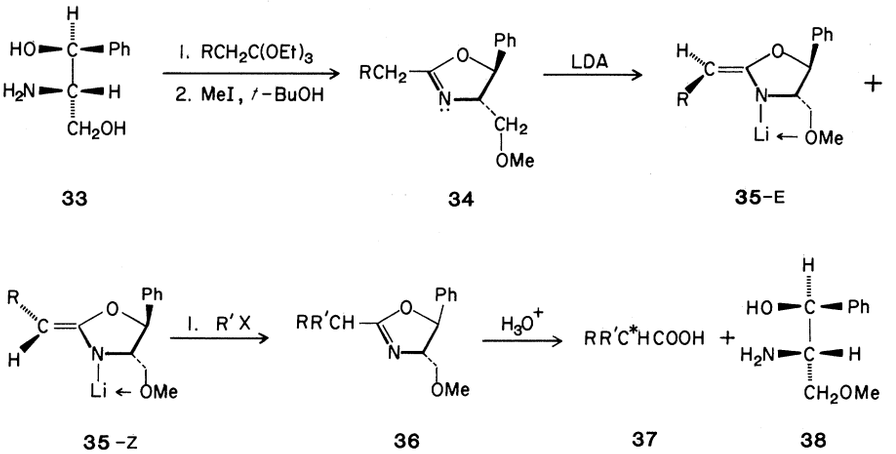


Fig. 7. Asymmetric alkylation with the chiral oxazoline system. *LDA*, lithium diisopropyl amide [LiN(*i*-pr)$_2$].

Grignard reagent, followed by hydrolysis, regenerates the chiral-inducing agent **28** and forms the α-hydroxy aldehyde **32** in enantiomeric excess of 84 to 98 percent. As in the oxathiane case, diverse R groups are available. This chiral aminal synthesis has been engineered in several different ways (*21*) and has been used to synthesize several natural products (*27, 45*).

Oxazoline system. Extensive studies by Meyers (*18*) and his students on chelation control in oxazoline systems has had a profound influence on developments in the field of asymmetric synthesis during the last decade. The oxazoline template is a versatile chiral adjuvant; its applications are among the most imaginative in the annals of asymmetric synthesis.

The basic oxazoline chiral-inducing agent is prepared in two steps from commercially available (1*S*,2*S*)-1-phenyl-2-amino-1,3-propanediol (**33**) (Fig. 7). In one of the early applications, this oxazoline (**34**; R, alkyl or aryl) was allowed to react with lithium diisopropyl amide (LDA) to yield a mixture of chelation-stabilized *E* and *Z* aza-enolates **35-*E*** and **35-*Z*** (5:95 ratio when R is CH_3). Treatment of the aza-enolate mixture (reaction with **35-*Z*** shown) with electrophiles (shown as R′X) results in the substituted oxazoline **36**, which can be hydrolyzed to give the chiral substituted acid **37** and the *O*-methyl derivative **38**. Oxazoline **34** is resynthesized from **38**, and the cycle is ready to be repeated.

The two crucial structural elements that determine the stereochemical control of this oxazoline system are the methoxy group and the *trans*-phenyl substituent. As shown in **35-*Z***, the methoxy group holds the enolate in a rigid conformation by chelation with the lithium while the phenyl group blocks the top face of the oxazoline ring. These factors force attack by the electrophilic R′ group from the bottom face.

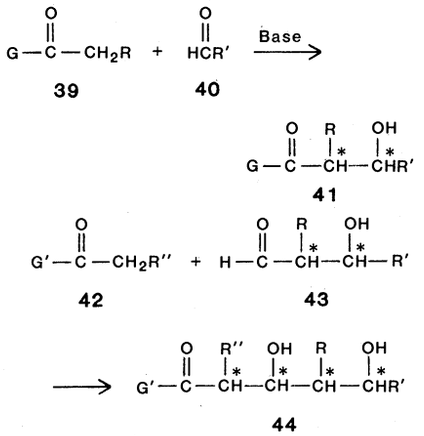
Numerous variants of the chirality transfer accomplished by this system have been reported (*18, 27, 45*). These reports include: 3-hydroxy- and 3-methoxy acids, 2-hydroxy-, 2-methoxy-, and 2-chloro acids, 3,3-dialkyl- and 2,3,3-trialkylpropanoic acids, 2-substituted butyrolactones and valerolactones, phthalides, thiolepoxides, dihydropyridines, and binaphthyls. A specific application of the oxazoline asymmetric synthesis is the preparation of the European pine sawfly pheromone (*45*).

Chiral Aldol Condensation Reactions

The aldol condensation appears frequently in both biosynthetic and laboratory synthetic sequences for the construction of complex molecules. The detailed facets of its stereochemistry make it potentially a powerful reaction for the synthesis of natural products, but realization of this potential has been elusive. Complexities of the reaction rendered it one of the most challenging problems in synthetic organic stereochemistry. Cram (*9*) made important contributions to the stereochemistry of the aldol condensation in the early 1950's; however, the diastereomer selection of this reaction is just now being brought under satisfactory synthetic control, based primarily on the work of Evans (*46*), Masamune (*47*), and Heathcock (*48*).

A simple crossed aldol condensation between the carbonyl compounds **39** and **40** leads to structure **41**, which with two chiral centers, exists in four isomeric forms. If the G group in product **41** is hydrogen (or can be replaced by hydrogen), then another aldol condensation

yields structure **44** with four contiguous chiral centers, which can exist in 16 isomeric forms. The extreme stereochemical complexities of the reaction are obvious. The isomers of **41** are *erythro*- or *threo*-type diastereomers, each of



which exists in either *d* or *l* enantiomeric forms. Thus two types of stereochemical control are involved: diastereomer selection to give predominantly either the *erythro* or *threo* form (control of the relative configuration of the two chiral centers) and enantiomer selection to give predominantly either the *d* or *l* isomer of the *erythro* or *threo* form (control of the absolute configuration of the two chiral centers).

The intricacies of the advances that have been made in the aldol condensation prevent an adequate treatment of its stereochemistry here. Accordingly we will make only a few general comments. If either of the carbonyl compounds **39** or **40** is already optically active by virtue of a chiral R group (that is, **39** or **40** has been obtained optically active by some independent method), then the enantioselectivity (control of absolute stereochemistry) is built into the reaction. However, there is need for a breakthrough in the asymmetric synthesis of the aldol condensation itself. Perhaps an effective and general chiral catalyst for the aldol condensation can be developed as has been for the allylic alcohol epoxidations. That this is not impossible is shown by the unique intramolecular aldol asymmetric synthesis catalyzed by L-proline discovered by Hajos and Parrish (*49*). Alternatively, it may be that a general effective reagent for preparing chiral enolates, involved as intermediates in the aldol condensation, can be developed. If so, then complete stereochemical control of this reaction would have been achieved.

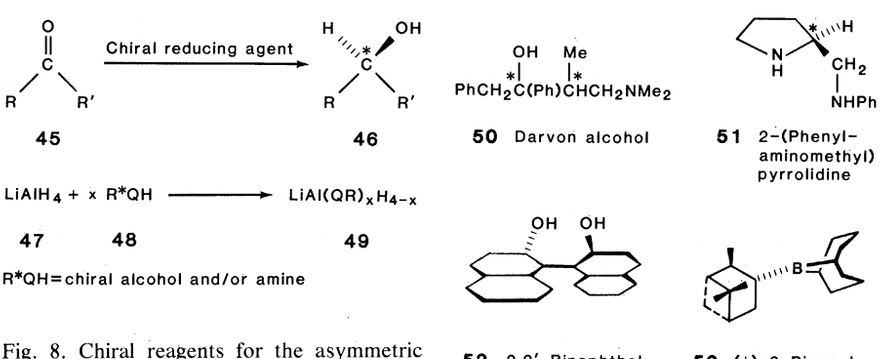


Fig. 8. Chiral reagents for the asymmetric reduction of ketones to secondary alcohols (*26*).

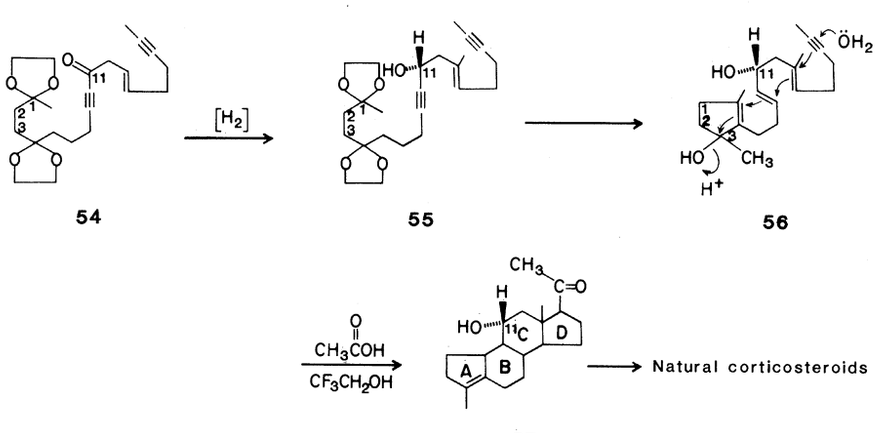


Fig. 9. Synthesis of chiral secondary carbinol **55** by asymmetric reduction of achiral ketone **54**, followed by polyene cyclization to the steroid precursor, **57**.

Asymmetric Reduction

An available, widely applicable, chiral reducing agent for the conversion of unsymmetrical ketones **45** into the corresponding chiral secondary carbinols **46**, with enantiomeric purities of better than 90 percent of either desired configuration, would be of great value (Fig. 8). Extensive research has resulted in several successful reagents (*4*, *26*, *27*, *50*, *51*) but none can be considered ideal. However, the results to date are sufficiently encouraging to allow the prediction that the problem will be successfully resolved in time.

The easiest chiral reducing agents to prepare and handle are those (**49**) generated from the reaction of lithium aluminum hydride (**47**) with a chiral ligand (R*QH; **48**). Examples of the most successful of such chiral ligands are the amino alcohol **50** (*50*), the diamine **51** (*21*), and the diol **52** (*51*). The reagent (*50*) from Darvon alcohol **50** is especially favorable for reduction of acetylenic ketones (*52*); chemical yields of 70 to 96 percent and stereochemical yields from 72 to 84 percent enantiomeric excess are observed. An example of the use of this reagent, as well as the borane reagent (*53*) from α-pinene and borobicyclo[3.3.1]nonane (**53**), is given in the polyene cyclization reaction illustrated in Fig. 9.

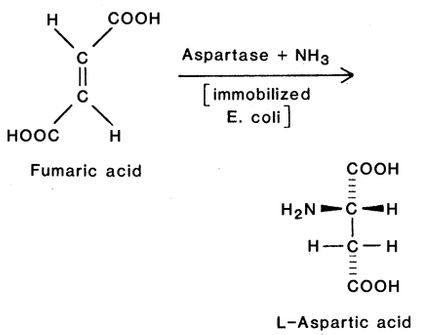
Polyene Cyclization

The potential of asymmetric synthesis as applied to steroids is being explored intensively. One of the most interesting systems is that of polyene cyclization which has been the subject of study by several groups, most successfully by Johnson and his co-workers (*54*, *55*). In the example shown in Fig. 9 the polyenediol **56** has two chiral centers, one at C-3 and the other at C-11 (according to steroid numbering). The one at C-3 is destroyed during the cyclization and apparently has no stereochemical influence on the reaction, but the other at C-11 carries through unchanged in the product. When the starting polyenediol **56** is a racemate, the product is a racemic mixture of the natural and unnatural enantiomers. When the pure 11-(*R*) enantiomer **56** is cyclized, the product **57** has the desired natural steroid configuration. Thus, once the chiral intermediate is at hand, the subsequent cyclization, forming six additional chiral centers, is directed to give only the one desired enantiomeric product. Accordingly, an efficient method of obtaining the chiral polyenediol **56** or its

precursor **55** is needed. Classical resolution of **55** failed in this case, but asymmetric reduction of the precursor ketone **54** was successful (*54*). The $LiAlH_2(OR^*)_2$ reagent made from **50** was used to reduce **54** in 78 percent chemical yield to give a 91:9 mixture of **55** and its C-11 enantiomer. A precursor acetylenic ketone that is related to **54** was reduced with the chiral (+)-α-pinene-9BBN reagent **53** (*53*) to give product with a 98.5-to-1.5 ratio of enantiomers (*55*).

Immobilized Enzymic Asymmetric Synthesis

In 1978, the Tanabe Seiyko Company in Japan went into commercial production of L-aspartic acid by a continuous process in which a buffered ammonia and fumaric acid solution was passed over a selected strain of *Eschericha coli* cells that were immobilized in a polysaccharide gel (*56*). The potential use of immobilized enzymes and immobilized



whole cells for production of chiral natural products seems limited only by economic factors and man's ingenuity in harnessing these natural systems. Furthermore, they serve as models of synthetic chiral catalyst systems not yet realized.

We have omitted many innovative and important developments in this general treatment of the current status of asymmetric synthesis. We are sorry that we have slighted so much good work; for example, one obvious omission has been the many applications of hydroboration in this field which is a subject by itself (*53*, *57*). We must also point out the article by Trost (*58*) in which stereochemical control of reactions, including enantioselectivity, is discussed.

We believe that the foregoing examples support the thesis that the science of asymmetric synthesis has come of age. Asymmetric synthesis must be systematically considered in any synthetic strategy aimed at the formation of chiral compounds.

References and Notes

1. Chiral molecules have the property of handedness [chiral from the Greek χειρ (*cheir*), meaning hand]. Chiral structures, like right versus left hands, have the same connections (connectivity); they are mirror images of each other, but they are not identical because they are not superposable on each other. An achiral structure lacks the property of handedness. A structure that is achiral but on further substitution becomes chiral is called prochiral.
2. W. A. Bonner, in *Exobiology*, C. Ponnamperuma, Ed. (North-Holland, Amsterdam, 1972), pp. 117–181.
3. The two enantiomeric forms of the amino acid, **2**-(*S*) and **2**-(*R*), have the same connectivity. However, they are not identical because of the way they are connected in three-dimensional space. To be identical, two structures must be superposable; **2**-(*S*) and **2**-(*R*) are not. As written **2**-(*S*) has the NH_2 group below the plane of the page, whereas **2**-(*R*) has it above. Reorientation of structure **2**-(*R*) by rotating 180° around the horizontal axis through the central carbon atom shows that **2**-(*S*) and **2**-(*R*) are mirror-image structures. Nonsuperposable mirror-image structures are known as enantiomers. A 50:50 mixture of enantiomers is called a racemate and is achiral in the aggregate.
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5. These numbers may not be a quantitatively accurate reflection of the research activity in this area because of both more efficient indexing by Chemical Abstracts Service and because of a change in their subject classifications, but the qualitative conclusion is valid.
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