31 May 1974, Volume 184, Number 4140 SCIENCE

Asymmetric Synthesis

Asymmetric synthesis allows facile preparation of many important chiral organic molecules.

John W. Scott and Donald Valentine, Jr.

Obtaining chiral molecules is a key problem in the synthesis of natural products, flavors, fragrances, and, particularly, pharmaceuticals. Recently, Morrison and Mosher (*1*) have reviewed the major methods for producing optically active compounds. These include physical separation via enantiomeric crystal forms, resolution based on physical separation of diastereomeric forms, thermodynamically controlled asymmetric transformations of stereochemically labile diastereomers, and kinetically controlled asymmetric transformations. This last category, asymmetric synthesis, has been defined as (*1*, p. 5): "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts." Asymmetric synthesis is the method of choice for obtaining chiral molecules since it permits the conversion of as much as 100 percent (depending on the degree of asymmetric induction) of a prochiral substrate to a chiral product. The economic implications of this fact are obvious. No less exciting, though, is the esthetic value of a well designed and executed asymmetric synthesis!

Asymmetric synthesis occurs because a reagent and substrate, at least one of which is chiral, form diastereomeric transition states which differ in energy. The magnitude of this difference in energy, $\Delta\Delta G\ddagger$, determines the excess of one enantiomer over the other [the enantiomeric excess, or e.e. (*2*)]. The reagents used may be chemical only, or enzymes or biological organisms. The challenge in chemical asymmetric synthesis is to devise reactions that will maximize $\Delta\Delta G\ddagger$. Typically, one attempts to achieve a large $\Delta\Delta G\ddagger$ by introduction of steric hindrance in the undesired pathway or by facilitation (or both), through some attractive interaction, of the lower energy pathway. These methods are, however, empirical and often unreliable, since the component enthalpy ($\Delta\Delta H\ddagger$) and entropy ($\Delta\Delta S\ddagger$) terms of $\Delta\Delta G\ddagger$ may change in different directions with, for example, a given change in substituent. Because of this, virtually no guidelines can be given as to how to design an asymmetric synthesis. It is logical, however, to pick an early step in the synthesis (in case enantiomeric excess of less than 100 percent is obtained) and to give careful consideration to choice of a substrate or reagent (or both) which should show maximal transition state interactions. A corollary to this proposal is that one should choose, if possible, a reaction whose mechanism is known, which has an ordered transition state without accessible symmetry elements, and which is already known to proceed generally in a stereoselective manner.

It is important, for both esthetic and practical reasons, to use chiral reagents efficiently. This would seem to require at least that the reagent used in a particular reaction be recovered. Only in special cases is it desirable to destroy one chiral center as part of the process of making another. The most effective use of chiral reagents is, of course, their use as catalysts. Several spectacular successes in this type of asymmetric synthesis have been reported, and we believe that chiral catalysts will come to occupy a preeminent position in the preparation of chiral molecules.

There are several recent reviews (*3*, *4*) of asymmetric synthesis. This article is concerned, therefore, primarily with recent work (that is, reported since early 1969) not covered by Morrison and Mosher (*1*). We have considered reactions which seemed to us to be useful as practical preparations of chiral molecules and offer at least some promise of being useful generally. The percent of enantiomeric excess that must be achieved to make an asymmetric synthesis useful varies with each case and depends on such factors as whether the desired product enantiomer can be obtained in good chemical yield by crystallization from a mixture with, for example, 10 to 15 percent of the wrong enantiomer. We consider in general, however, that less than a 50 percent enantiomeric excess (3 : 1 mixture) is probably not useful except in special cases. We have organized the material presented below as much as possible according to the functional group which undergoes reaction. The hope is that this organization will give an idea as to what can be accomplished with the different functional groups and thereby prove useful in choosing at what stage to introduce chiral centers in multistep syntheses.

Olefin Reactions

Modified enamine alkylation via the iminium salt (*5*) of the imine **1** (Fig. 1) derived from cyclohexanone and (−)-bornylamine with methyl iodide gave after hydrolysis (*S*)-2-methylcyclohexanone (**2**) in 72 percent enantiomeric excess (*6*). In a mechanistically

The authors are members of the Chemical Research Department of Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

Table 1. Chiral amino acids by enantioselective catalytic hydrogenation. The data are taken from reference (*31*). Various Rh compounds can be used to generate the catalyst. These include Rh^{I} olefin complexes and phosphine, $RhCl_3$ and phosphine, or preformed complexes such as $[Rh(norbornadiene)(phosphine)_2]^+ClO_4^-$. Also, various bases, such as sodium methoxide and piperidine, have been used. The optical yield may depend on the base used. The exact details of how the optical yields reported below were obtained have not, in all cases, been described.

R_1	R_2	Enantiomeric excess*	Resulting amino acid†
3-(1-Acetylindoyl)	C_6H_5	90	(*S*)-Dopa
$3\text{-}CH_3O\text{-}4\text{-}CH_3COO\text{-}C_6H_3$	CH_3	88	(*S*)-Dopa
C_6H_5	CH_3	85	(*S*)-Phenylalanine
C_6H_5	C_6H_5	85	(*S*)-Phenylalanine
$4\text{-}Cl\text{-}C_6H_4$	CH_3	77	(*S*)-p-Chlorophenylalanine
3-(1-Acetylindoyl)	CH_3	80	(*S*)-Tryptophan
H	CH_3	60	(*S*)-Alanine

* The chemical yields are usually virtually quantitative. † After acyl and (in the case of the dopa precursors) methoxyl cleavage.

similar reaction, treatment of the chiral oxazoline **3** (*7*) with lithium diisopropylamide resulted in selective removal of one of the prochiral methylene protons. Alkylation of the resultant chelated lithio salt **4** occurred on the unhindered top face to give after acid hydrolysis the (*S*)-α-methylcarboxylic acids, **5** (60 to 67 percent enantiomeric excess), as well as amino alcohol from which the oxazoline could be regenerated. This method, which is apparently limited at the present time to α-methyl acids, also gave (*R*)-acids from the enantiomeric oxazoline.

Several uses of enamines derived from carbonyl compounds and optically active amines in asymmetric syntheses have been reported. Particularly favored as amine components have been esters and amides of proline. Thus, bromination of cyclohexanone ethyl prolinate enamine gave 2-bromocyclohexanone in 37 percent enantiomeric excess (*8*). Michael reaction of the same enamine with methyl acrylate or acrylonitrile gave alkylated products in up to 59 percent enantiomeric excess (*9*, *10*). Similar reaction with the enamine **6** from 4-methylcyclohexanone gave an interesting result in that formation of the enamine itself resulted in an asymmetric synthesis (*11*). Introduction of the enamine double bond occurred regioselectively to give predominantly the diastereomer, **6**. Subsequent Michael reaction and hydrolysis gave a mixture containing 83 percent of the *cis*-(2*R*,4*S*) product, **7**, along with 17 percent of its *trans*-(2*S*,4*S*) isomer. Unfortunately, the percent enantiomeric excess was unknown. An asymmetric synthesis of cyclohexenone derivatives (*12*) is exemplified by reaction of enamine **8** with methyl vinyl ketone followed by cyclization. This type of reaction has been employed (*13*) as a key step in the asymmetric synthesis of the unnatural (+)-antipode of the alkaloid mesembrine (percent enantiomeric excess unknown). Extension of the method to the synthesis of (*R*)-$\Delta^{1(9)}$-2-octalone (percent enantiomeric excess unknown) has been reported (*14*).

Intramolecular acylation of the vinylogous amides obtained from proline derivatives and cyclohexane-1,3-diones gave products related to the mitomycin antibiotics in low enantiomeric excess

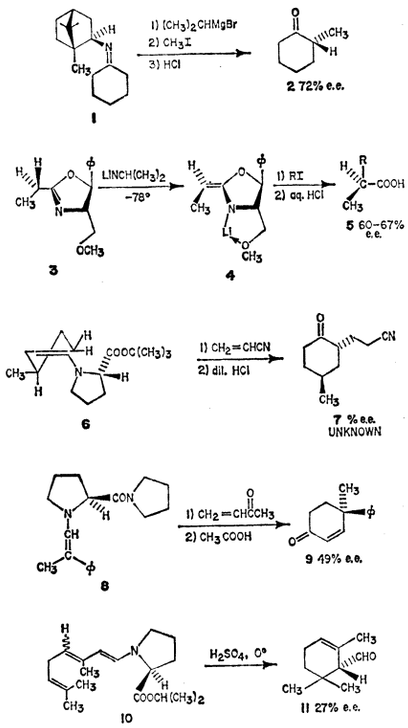
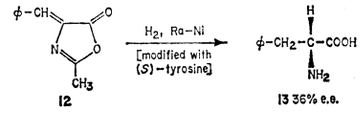


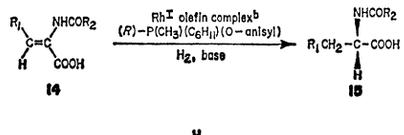
Fig. 1. Asymmetric syntheses via imines and enamines.

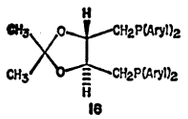
(*15*). Cyclization of the dienamine **10** from citral gave (*S*)-α-cyclocitral [**11**, 27 percent enantiomeric excess (*16*)]. Acid cyclization of optically active esters of the homologous homogeranic acid gave *cis*-tetrahydroactinidiolide in up to 41 percent enantiomeric excess (*17*). [2,2] Cycloaddition to an enamine in 25 percent enantiomeric excess (*18*), and addition of the morpholine enamine of cyclohexanone to menthyl crotonate (percent enantiomeric excess unknown) (*19*) have also been reported. Although the enamine reactions usually give rather low chemical yields, they allow creation of asymmetric centers that are in the alpha position to a carbonyl group (*20*) despite the relatively easy racemization of these centers through enolization. It is somewhat surprising a priori that the enamine hydrolysis step can be carried out without racemization and, in fact, it has been found (*6*, *8*, *9*) that careful attention to experimental detail is required to obtain high enantiomeric excesses.

The use of catalytic asymmetric hydrogenation of prochiral olefins to prepare chiral molecules has been one of the most widely studied asymmetric reactions (*1*, pp. 292–294 and 297–299; *4*, *21*). Initial work in this area involved heterogeneous chiral catalysts such as palladium on silk or Raney metal modified by added chiral organic substances. An example of this type of reaction, in which the enantiomeric excesses are usually less than 50 percent, is the synthesis of phenylalanine **13** from **12** (*22*). This work has been reviewed (*23*), and there is active continuing interest in this problem (*24*). The related approach of hydrogenation of a chiral olefin followed by removal of the original asymmetric center has also continued to draw attention. The hydrogenation of arylidine derivatives of glycyl-(*S*)-proline has been shown (*25*) to proceed with a high (> 80 percent) stereoselectivity. Subsequent acid cleavage of the resultant diketopiperazines gave aromatic amino acids in good yield. The related synthesis of methyl aspartate (98 percent enantiomeric excess) (*26*) apparently lacks generality and that of alanine (*27*) suffers from a low (6.5 percent) enantiomeric excess.

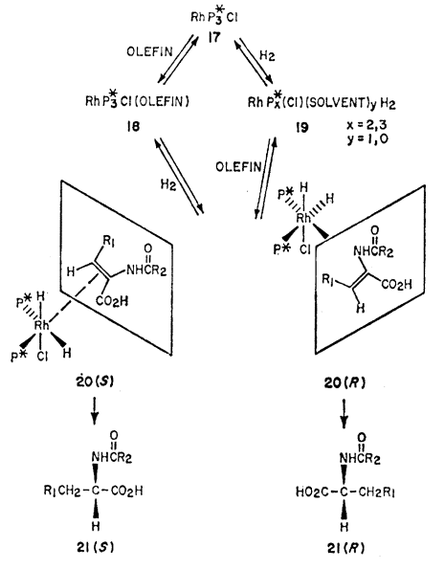


A major problem with the modified insoluble catalysts is that the nature of the active sites on the catalyst is not known in detail. As a result, it is difficult to predict how a given modification will change the catalyst. Furthermore, the homogeneity of the catalyst is not assured. A somewhat more detailed understanding of how certain soluble hydrogenation catalysts function (*28*, *29*) has led to some of the most exciting developments in asymmetric synthesis. These catalysts have been particularly effective in asymmetric olefin hydrogenation. Knowles *et al.* (*30*, *31*) have found (Table 1) that a variety of amino acids can be obtained by hydrogenation of the corresponding α-amidocinnamic acids **14**. Their technique involved the use of soluble rhodium (I) [Rh^I] complexes of chiral phosphines (*32*), in particular (*R*)-*o*-anisylcyclohexylmethylphosphine, as catalysts. Several of the reactions described are of obvious commercial significance. For example, simple crystallization of the crude (*S*)-dopa (dihydroxyphenylalanine) obtained in the first two examples of the table gave this important drug (which is used to alleviate symptoms in Parkinson's disease) in essentially optically pure form. Kagan (*33*, *34*) has shown that similar results can be obtained with the more easily prepared diphosphines **16**, which are derived from tartaric acid.





The role of the chiral phosphine can be seen by consideration of the plausible reaction mechanism (*28*) shown in Fig. 2. As indicated, two diastereomeric intermediates [**20**(*S*) and **20**(*R*)] are formed during the hydrogenation of the prochiral α-amidocinnamic acid. It can be presumed from studies of various nonchiral systems that these intermediates collapse in a rate limiting step involving synchronous (or rapid stepwise) hydrogen transfer from the metal to the coordinated face of the olefin. Since, in this case, the formation of **21**(*S*) is highly favored, clearly the hydrogen transfer from **20**(*S*) proceeds via a lower energy transition state than



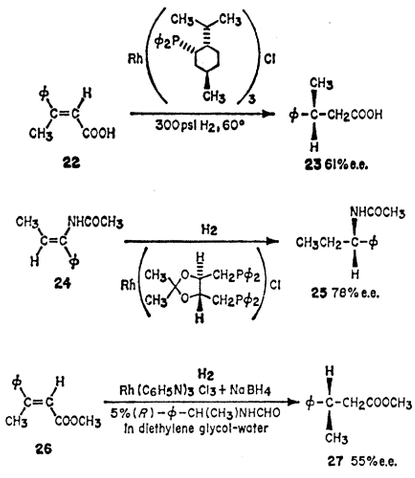


Fig. 2 (left). Hydrogenation of (*Z*)-$R_1CH{=}C\text{-}(NHR_2)COOH$ by a Rh^I catalyst containing chiral phosphines (P*). Fig. 3 (right). Asymmetric olefin reductions with soluble catalysts.

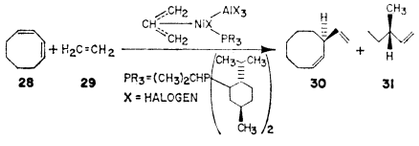
in the corresponding reaction of **20**(*R*). In the study by Knowles *et al.*, it may well be that, in addition to the expected steric effects, attractive interactions between the amido group of the substrate and the ortho methoxyl group of the phosphine ligand contribute to the observed $\Delta\Delta G\ddagger$. Similar interactions can be postulated for the diphosphine ligand **16**. The addition of base to the reaction medium leads to the formation of carboxylate anions which may coordinate to the metal, thus further anchoring the substrate, with a resultant effect on the asymmetric course of the reaction. In addition, the ratio of chiral phosphine (P*) to rhodium, temperature, solvent, hydrogen pressure, and type of added base all affect the enantioselectivity of the reaction. This suggests that many equilibria are involved and that careful optimization not only of the phosphine, but also of the conditions, is required to obtain high enantioselectivity. Unfortunately, this optimization must be arrived at empirically since little is known of the actual transition state. Selection and synthesis of the proper phosphine, for example, is probably the true "rate limiting step" in catalytic asymmetric synthesis!

These considerations suggest that a fairly sensitive "symbiosis" between substrate and phosphine must be established. α-Amidocinnamic acids are probably favored substrates in this respect since they are comparatively rich in functional groups that can interact with suitable phosphines. In addition they are strongly activated compared to other trisubstituted olefins, with the result that they can be hydrogenated homogeneously under a variety of conditions. Nevertheless, additional substrates (Fig. 3) have been hydrogenated by this technique with good enantioselectivity. The synthesis of compounds **23** (*35*), **25** (*34*), and **27** (*36*) illustrate the variety of catalytic systems that can be employed. The active catalyst involved in producing compound **27** is probably a rhodium (III) hydride containing coordinated chiral amide. This is potentially a very attractive system because a number of chiral amides are readily available and the catalyst will hydrogenate many olefins that are unreactive to $Rh(P\phi_3)_3(Cl)$, where ϕ is a phenyl group. Finally, in an analogous reaction it was claimed (*36*) that both *E* and *Z* methyl β-methylcinnamate gave (*S*)-methyl 3-phenylbutyrate in 40 and 45 percent enantiomeric excess, respectively. It was suggested that hydrogen transfer occurred after the *E* and *Z* distinction had been lost.

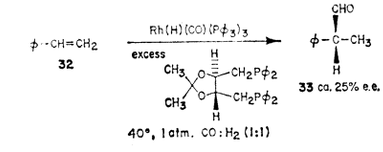
It is worthwhile at this point to comment briefly on the probable future role of so-called "hybrid heterogeneous-homogeneous catalysts" (*37*) in asymmetric hydrogenations and other reactions. These catalysts can be of two types: (i) an optically active polymer support to which is attached a typical soluble, metal complex group [such as $Rh(P\phi_3)_3(Cl)$ derivatives attached to cellulose through one of the phosphines as described in a recent patent (*38*)]; (ii) an optically inactive support to which are attached chiral phosphines which can bind Rh atoms (for example, phosphines analogous to **16**). Rhodium complexes of these polystyrenes are

catalysts for various asymmetric reactions (*39*). These hybrid catalysts have the advantages of both homogeneous (well-defined catalytic sites) and heterogeneous (easy separation and recovery) catalysts, and it can be predicted with certainty that this area will receive a great deal of attention during the next few years.

Hydrogenations are not the only reactions subject to asymmetric homogeneous catalysis. For example, cooligomerization of ethylene and 1,3-cycloctadiene catalyzed by π-allyl nickel halide-aluminum halide-chiral tertiary phosphine combinations gave optically active **30** and **31** (*40*). The



highest enantiomeric excess of **30** was 70 percent, obtained at 0°C with a P* : Ni ratio of 38 : 1. With methyldimethylphosphine the enantiomeric excess of **30** was 53 percent at −75°C, but only 23.5 percent when the reaction was performed at 0°C. The highest enantiomeric excess obtained for 3-methylpentene (**31**) was 64 percent. Formation of optically active **31** in this reaction is an attractive result since hydroformylation of this material has been shown to give 4-methylhexenal without racemization (*41*). Asymmetric hydroformylations of prochiral olefins have been the object of numerous investigations (*42, 43*). In general, the products of the reactions contained low enantiomeric excesses. The most successful reaction yet developed is the conversion of styrene to hydratropaldehyde (**33**) of about 25 percent enantiomeric excess (*43*). The asymmetric hydrocarboxylation of olefins in low (<15 percent) enantiomeric excess has recently been demonstrated (*44*).



Another method for producing a chiral center during C-C bond formation has been developed by Trost and Dietsche (*45*). Thus, alkylation of *syn, syn*-1,3-dimethyl-π-allyl-palladium chloride dimer with diethyl sodiomalonate in the presence of (+)-*o*-anisylmethylcyclohexylphosphine gave diethyl (*E*-

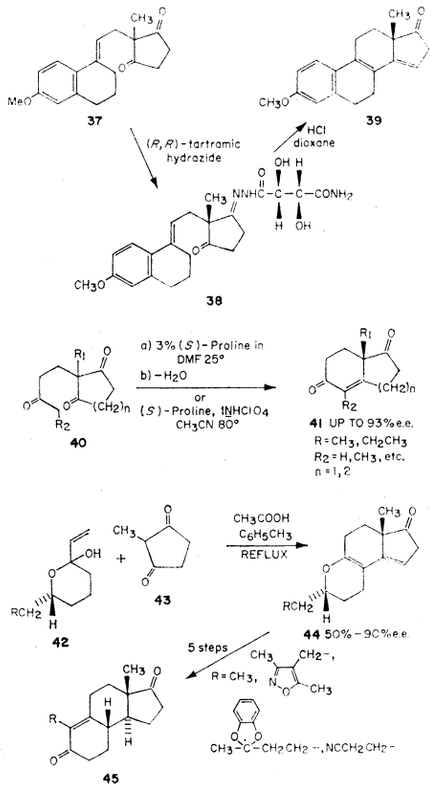


Fig. 4. Asymmetric steroid syntheses.

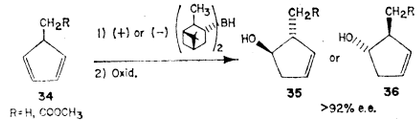
hex-2-en-4-yl)malonate in good yield. Subsequent reactions converted this material to (*S*)-ethyl *E*-3-methyl-4-hexenoate having a 24 percent enantiomeric excess. In a related reaction, coupling of (*R,S*)-α-methylbenzylmagnesium bromide with vinyl chloride in the presence of a chiral nickel complex gave (*R*)-3-phenyl-1-butene in 17 percent enantiomeric excess (*46*).

Several other asymmetric syntheses fall into the scope of this discussion of the use of metals with chiral ligands as catalysts or intermediates. Optically active alkyl chrysanthemates (as a mixture of *cis* and *trans* isomers) are claimed as products of the decomposition of ethyl diazoacetate in the presence of tetramethylallene and catalytic amounts of copper complexes of chiral ligands (*47*). Similar reactions catalyzed by bis-[*N*-(*R* or *S*)-α-phenethylsalicylaldiminato]-copper (II) with various olefins have been reported (*48*). A modified Simmons-Smith reaction in the presence of menthol has been described (*49*). These processes all gave products of low optical purity.

The synthesis of β-hydroxy esters by the Reformatsky reaction in the presence of sparteine gave products in up to 95 percent enantiomeric excess (*50*). The conjugate addition of an alkyl-copper-sparteine complex to α,β-unsaturated ketones gave products in enantiomeric excess up to 6 percent (*51*).

Asymmetric deuteration (54 percent enantiomeric excess) of the α-carbon of (*S*)-aspartic acid has been achieved through the template action of a disymmetric Co^{III} complex (*52*).

Asymmetric hydroboration continues to be an excellent method for converting prochiral olefins to chiral molecules. Although the subject has been thoroughly reviewed (*53*), two new examples merit attention. Hydroboration of the cyclopentadienes **34** with either



(+)- or (−)-diisopinocampheylborane, followed by oxidation, gave the alcohols **35** or **36**. In each case, the products were of more than 92 percent enantiomeric excess. The product **35** (R = H) was converted to loganin (*54*) while compound **35** (R = $COOCH_3$) was readily transformed in good yield (*55*) to key intermediates in total syntheses of the prostaglandin $PGF_{2\alpha}$ (*56*). Attempts to effect asymmetric olefin hydration in the opposite (that is, Markovnikov) sense by oxymercuration with mercuric salts of chiral acids and subsequent reduction (*57*) yielded products of low optical purity.

Carbonyl Reactions

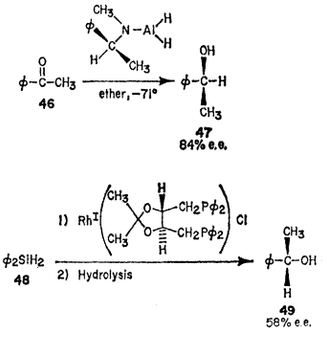
Selective reaction of one carbonyl group in prochiral 2-alkyl-2-methylcyclopentane-1,3-diones has led to several interesting new approaches to the asymmetric synthesis of 19-norsteroids (Fig. 4). Reaction of the dione **37** with (*R,R*)-tartramic hydrazide (*58*) led to percipitation of diastereomer **38** (75 percent yield of optically pure compound after recrystallization). Acid cyclization of this material (apparently with some racemization) gave the tetracyclic steroid intermediate **39**. Similar reaction with the 6-thia analog of **37** (*59*) gave again one enantiomeric hydrazone. This material could not be cyclized without complete racemization. However, permethylation followed by cyclization gave the 6-thia tetracyclic compound in 80 percent enantiomeric excess. (*S*)-2-Aminooxy-3,3-dimethylbutyric acid has been reported (*60*) as a second useful reagent (58 percent

enantiomeric excess) in this type of synthesis.

Two groups of investigators have independently reported (*61, 62*) that cyclization of the triones **40** lead to the bicyclic enediones **41** in high asymmetric yield. Initial attempts to cyclize **40** ($R_1 = CH_3$, $R_2 = H$, $n = 1$) with α-methylbenzylamine (*62*) gave **41** of 45 percent enantiomeric excess. When an amino acid (for example, proline or phenylalanine) was employed in the presence of perchloric acid at 80°C, the product contained an 84 percent enantiomeric excess of **41**. It was shown (*61*), however, that the mineral acid is not necessary in all cases, and that as little as 3 mole percent of (*S*)-proline in dimethylformamide at 25°C gives, after dehydration of an intermediate ketol, a virtually quantitative yield of **41** in 93 percent enantiomeric excess. Compound **41** has been used in an elegant synthesis of 19-norandrost-4-ene-3,17-dione (*63*). Use of this type of cyclization in an estrone synthesis (58 percent enantiomeric excess) has been reported (*64*).

Based on prior work with racemic compounds (*65*), Saucy and Borer (*66*) showed that condensation of the internally hydrated δ-hydroxyvinyl ketone **42** ($R = CH_3$) with 2-methylcyclopentane-1,3-dione gave the *trans*-dienol ether **44** in up to 90 percent enantiomeric excess. A five-step set of conversions, in which the original center of asymmetry was destroyed, led to the tricyclic enedione **45**. Use of ketone **42**, in which *R* was a protected 3-oxobutyl group (*67*) led by the same process (up to 78 percent enantiomeric excess) to tricyclic enediones **45** which could subsequently be converted to 19-norsteroids. A modification (*68*) of this synthesis has allowed the preparation of estrone precursors (78 percent enantiomeric excess).

The reactions of achiral carbonyl compounds with chiral reagents, and of chiral carbonyl compounds with achiral reagents (*1, 4*) continues to be of interest from both practical (*69*) and theoretical (*70*) viewpoints. A special case of the former type of reaction is reduction of the carbonyl group to carbinol with asymmetric reagents (*71*). A number of new or modified reagents have been developed (*72*) for this purpose. One such material, *N*-(α-methylbenzyl)-*N*-methylaminoalane (*73*) is highly enantioselective at −71°C, reducing acetophenone (**46**) to (*S*)-methylphenylcarbinol (**47**) of 84 percent enantiomeric excess. Heterogenous asymmetric hydrogenation of the C=O bond as an alternate means of reduction, has been widely studied (*23*), especially in the case of acetoacetic acid esters. More recently, asymmetric homogeneous reductions of carbonyl groups have been reported (*74*) but, except for the rather special case of the reduction of benzil to benzoin in 61 percent enantiomeric excess with Co(dimethylglyoximato)$_2$(quinine) as catalyst (*75*), the product alcohols are obtained with a low enantiomeric excess. Homogeneous catalytic asymmetric hydrosilylations of olefins and ketones have been demonstrated by several groups (*39, 76*). Enantiomeric excesses of up to 58 percent have been obtained. In the preparation of **49**, es-



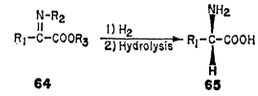
sentially the same enantiomeric excess was obtained with the Rh^I complex in homogeneous media or with a related Rh^I complex of the same phosphine bonded, at the 2 position of the dioxolane ring to polystyrene (*39*).

A major new area of asymmetric synthesis that has recently been developed is the use of reagents asymmetric at sulfur (*77*) to obtain compounds asymmetric at carbon (Fig. 5). Johnson has described the use of (*R*)-*S*-methyl-*S*-phenyl-*N*-(*p*-tolylsulfonyl)sulfoxime (*78*) and (*R*)-(*N,N*-dimethylamino)methyl-*p*-tolyloxo-sulfonium fluoroborate (*79*) as reagents for the asymmetric transfer of a methylene unit to ketones or aldehydes to form oxiranes, to imines to form aziridines, and to α,β-unsaturated ketones or esters to form cyclopropyl ketones or esters. The former reagent appears to be the one of choice since it, for example, converts *trans*-benzalacetophenone (**50**) to (1*R*, 2*R*)-1-benzoyl-2-phenylcyclopropane (**51**) in 49 percent enantiomeric excess, whereas the latter reagent yields a product having the opposite absolute configuration in only 36 percent enantiomeric excess. A related reaction, involving formally the transfer of an ethylene unit, consists of the reaction of the sulfoximine salt **52** with a dibasic nucleophile such as **53** to give the cyanocyclopropane ester **54** (*80*). The initial step in this reaction is a Michael-type addition of the anion of **53** to the vinyl sulfoximine. Similar additions to asymmetric vinyl sulfoxides followed by reductive removal of the sulfur have also been described (*81*). The most successful reaction of this type was the addition of diethyl malonate to vinyl sulfoxide **55** (*82*) to give diastereomer **57** in 60 percent enantiomeric excess. The pure diastereomer **57**, isolated in 51 percent yield by crystallization, was converted in four steps to (*S*)-3-phenylbutyric acid (**58**), a precursor of the natural amino acid 2-amino-3-phenylbutyric acid.

An alternate approach to the use of asymmetric sulfur reagents involves addition of the anion of an optically active sulfoxide to an appropriate substrate (usually a ketone or aldehyde) followed by destruction of the asymmetry at sulfur (*83*). A sulfoxide commonly used (*84*) because of its availability is (*R*)-methyltolyl sulfoxide (**59**). Reaction of this material with α-tetralone gave the β-hydroxy sulfoxide **60** in 28 percent enantiomeric excess (*84*). Reduction with Raney nickel then gave optically active 1-methyl-1-tetralol (**61**). Similar reaction of sulfoxide **59** with *N*-benzylideneaniline gave only one disastereomer of **62**, which was then reduced to amine **63** (*85*).

Imine Reactions

Asymmetric reactions of enantiotopic or diastereotopic faces of a C=N bond have been developed largely because of the desire for ready access to optically pure amino acids (*86*). This field received a good deal of attention during the early 1960's from the observations that hydrogenation of the imines **64** (R_2 or R_3, or both, optically active) followed by hydrogenolysis (R_2 was generally benzylic) and saponification gave amino acids **65** in fair to excellent enantiomeric excesses. This process, termed



64 65

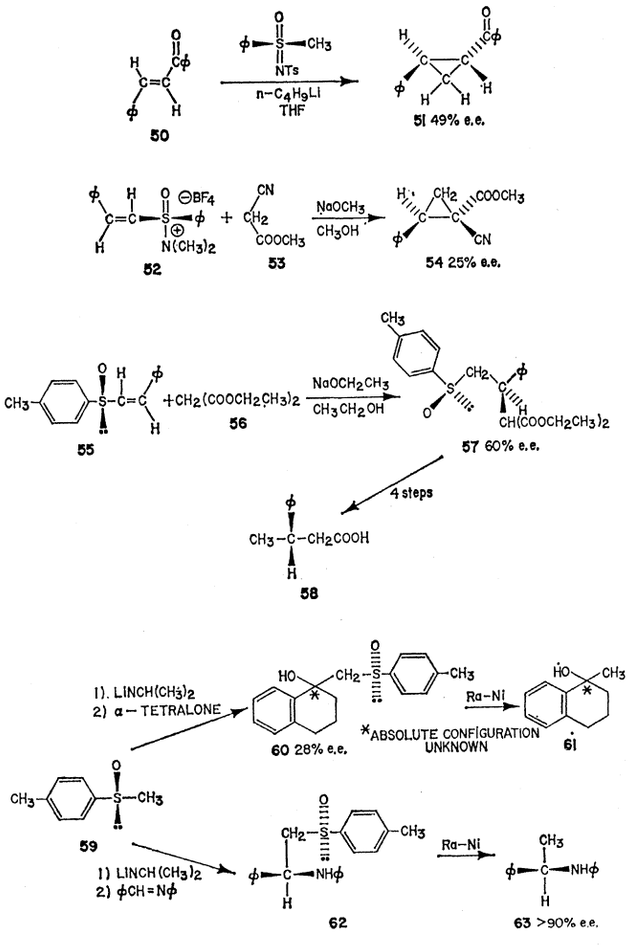
"asymmetric transamination," continues to be of interest (*87*), in particular with regard to defining the conditions necessary to obtain maximum enantio-

meric excesses (*88*). Use of boranes as reducing agents in place of hydrogen has been reported (*89*) to give no improvement in the enantiomeric excesses of the product amino acids. Linking the groups R_2 and R_3 of structure **64** in a ring has been shown (*26, 90*) to give intermediates leading to amino acids in very high enantiomeric excesses. The reagent of choice is 1-amino-(*S*)-2-[(*R*)-1-hydroxyethyl]indoline (**66**, Fig. 6) (*91*), which reacts with substituted alkyl glyoxalates to give the hydrazino lactones **67**. Aluminum amalgam reduction of the C = N bond, hydrogenolysis of the *N-N* bond, and saponification gave the (*R*)-amino acids **68** in 96 to 99 percent enantiomeric excess. Interestingly, the hydrazine **66** of opposite configuration at the carbinol center also gives (*R*)-amino acids (92 to 96 percent enantiomeric excess).

Hydrogenation of prochiral imines **64** over asymmetrically modified heterogeneous catalysts has been reported (*1*, p. 303). We are unaware of any corresponding homogeneous examples (*92*). A reaction that accomplishes the same purpose, though, is the asymmetric hydrosilylation of imines with soluble rhodium catalysts (*93*). The product silylamines were not isolated. Acid hydrolysis of the reaction mixture gave amines of up to 65 percent enantiomeric excess.

Several asymmetric syntheses of amino acids are based on nucleophilic addition to an imine. Foremost among these is the Strecker synthesis (*1*, p. 327), in which cyanide is added to the imine from a chiral benzyl amine to give, after nitrile hydrolysis and hydrogenolysis of the benzyl group, amino acids in 22 to 58 percent enantiomeric excess (*94*). Study of this reaction has shown (*95*) that the previously reported (*96*) 98 to 99 percent enantiomeric excesses were due to fractionation during purification. Recent modifications involving benzoyl cyanide (*97*) or addition to a complex of borane and nitrile (*98*) gave no improvement in the degree of asymmetric synthesis. The use of amines other than α-methylbenzylamines in Strecker syntheses has begun to receive attention (*99*). One such base is (*S,S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**70**) (*100*) which reacted stereospecifically with **69** to give aminonitrile **71**. Acid hydrolysis (giving **72**), followed by basic oxidation over Raney nickel, acid hydrolysis, and HBr cleavage of the methoxyl groups gave (*S*)-α-methyldopa (**73**) in 85 to 90 percent enantiomeric excess. Unfortunately, the synthesis is applicable only to ketones, since the oxidation step causes racemization of lactones **72** derived from aldehydes. When the amine **70** is reacted with alkyl methyl ketones, a truly amazing asymmetric result occurs (*101*). It is claimed that alkyl groups with an even number of carbon atoms give (*S*)-amino acids, while those with an odd number of carbon atoms yield (*R*)-amino acids! No explanation for this result has been given.

A reaction related to the Strecker synthesis in that it also involves nucleophilic addition (in this case of an isonitrile) to an imine is the four component condensation developed by Ugi (*102*). Of particular interest is the use of chiral α-methylferrocenylamines (*103*) to form the imines. At the end of the sequence, the ferrocenyl group is removed by acid. The cleaved ferrocene derivative, upon treatment with



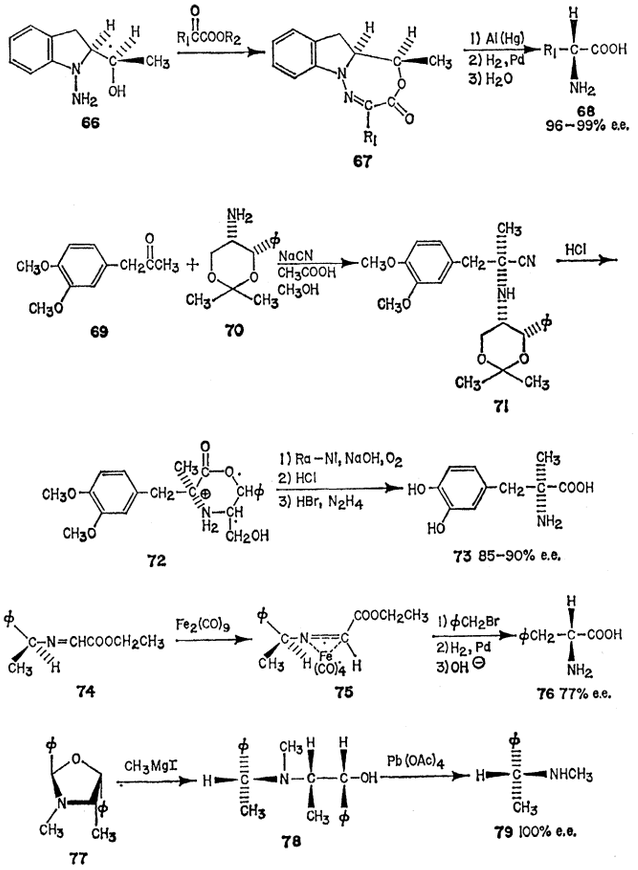


Fig. 5 (left). Use of chiral sulfur reagents in asymmetric syntheses. Fig. 6 (right). Asymmetric syntheses of amino acids and amines.

ammonia, regenerates the optically pure chiral amine (*104*). The enantiomeric excesses obtained with (*R*)- or (*S*)-α-methylferrocenylamine are about the same as with α-methylbenzylamine. However, it is reported (*102*) that 2-alkyl-α-methylferrocenylamines (*105*) give higher enantiomeric excesses. Details have not yet appeared. The use of chiral α-methylferrocenylamines as intermediates in other asymmetric syntheses seems attractive, especially since this reagent can be regenerated after use.

The addition of Grignard (*106*) or alkylcadmium (*107*) reagents to the α-methylbenzyl imine of menthyl glyoxalate gave amino acids of up to 64 percent enantiomeric excess. An interesting alternative approach (*108*) involved converting the imine from electrophile to nucleophile. Reaction of imine **74** with $Fe_2(CO)_9$ gave the adduct **75** plus small amounts of the "double bond" isomer. Alkylation of **75** with bromobenzene, followed by hydrogenolysis and hydrolysis, gave (*R*)-phenylalanine (**76**) in 77 percent enantiomeric excess. The synthesis of an amino acid by addition of another amino acid to an oxazolinone, followed by cleavage of the resulting dipeptide, has been reported (*109*). Neber rearrangement of *N*-chloroimidates prepared with menthol gave amino acids of up to 75 percent enantiomeric excess (*110*).

The reductions of imines to amino acids described above are also applicable to the preparations of chiral amines from the appropriate substrates (*111*). High enantiomeric excesses in the products were observed in several cases (*112*).

An interesting synthesis of chiral benzylamines is based on the observation that benzaldehyde reacts with ephedrine to give the oxazolidine **77** in over 90 percent yield (*113*). Treatment of this material with a Grignard reagent—for example, methylmagnesium iodide—gave the amine **78**. Lead tetraacetate cleavage of **78** gave (*R*)-*N*,α-dimethylbenzylamine. Other reactions of **78** gave (*R*)-*N*,*N*,α-trimethylbenzylamine and (*S*)-α-methylbenzyl bromide. It has been claimed that the reaction sequence is limited to aromatic aldehydes. However, the finding (*114*) that two racemic cyclopropane carboxaldehydes and a substituted cyclobutanone gave oxazolidines (also only one epimer at the new asymmetric center) indicates that this may not be necessarily so.

Intramolecular Transfer of Asymmetry

A special group of asymmetric syntheses are those in which a molecular rearrangement leads to the transfer of asymmetry to a new center within the molecule. Such processes usually involve destruction of the original chiral center and have thus been termed "self-immolative" (*115*). The reactions of this type which have shown the most synthetic potential to date can be classified as [3,3] sigmatropic rearrangements. Previously reviewed (*1*, pp. 375–379) examples include the "ortho-Claisen," Cope, Cope-Carroll, and aliphatic "aza-Claisen" rearrangements.

Modified aliphatic Claisen rearrangements involving triethylorthoacetate (*116*) and 1-methoxy-1-dimethylaminoethylene (*117*) occur with a high degree of stereoselectivity to give virtually exclusively *trans*-olefinic products. The high stereoselectivity can be rationalized in terms of a concerted process involving a chairlike transition state (*118*). It has now been found (*119*) that a concomitantly high degree of transfer of asymmetry is realized in these reactions. For example, reaction of the (*S*)-alcohol **80** (Fig. 7) with trimethyl orthoacetate gave the *trans*-(*S*)-acid **81** with an asymmetric transmission of at least 90 percent.

Somewhat more complicated, but highly illustrative examples of this type of reaction are provided by the work of Sucrow *et al.* (*120*). The diastereomeric acetylenic carbinols **82** and **83** were reduced to the *trans* (**84**, **86**) and *cis* alcohols (**85**, **87**). Reaction of these materials with 1-(dimethylamino)-1-methoxy-l-propene led, via the intermediates **88** to **91**, to the amides **92** to **95**. All products had a *trans* double bond. However, the configuration at C-24 of the product was determined by both the C-22 and double bond configurations of the starting material. Thus, the (22*R*)-*trans* (**84**) and (22*S*)-*cis* (**87**) compounds both gave (24*R*) products. Similarly, **85** and **86** gave the (24*S*) products **93** and **94**. This result has important practical implications for synthesis because both enantiomers of a resolved acetylenic carbinol can be

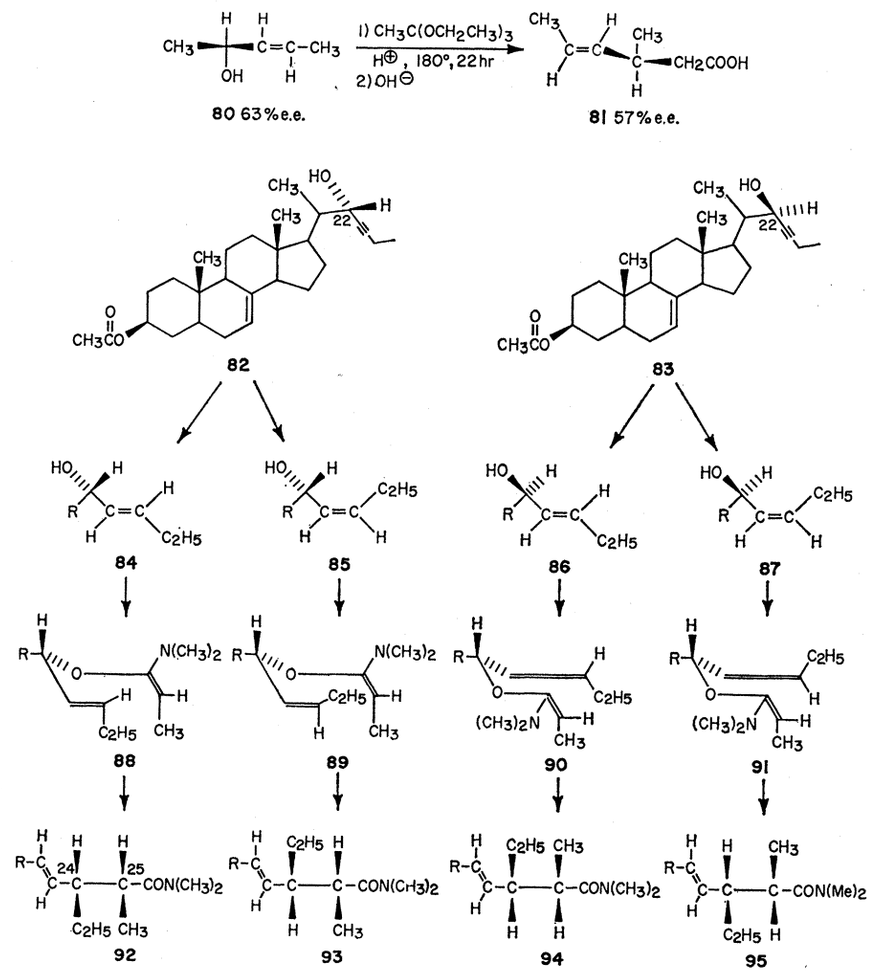
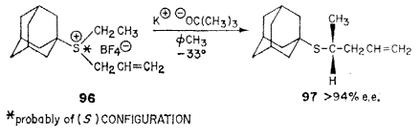


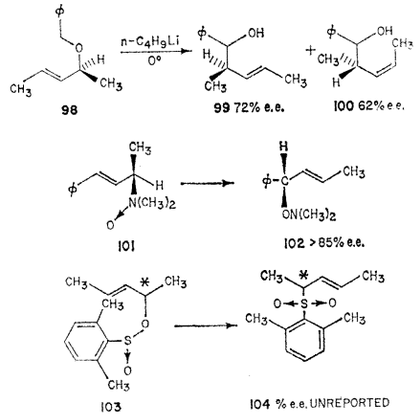
Fig. 7. Intramolecular transfer of chirality during modified Claisen reactions.

converted to the same Claisen rearrangement product. The products **92** to **95** contained up to 10 percent of material enantiomeric at C-25, which can be ascribed to the presence of small amounts of the *E* isomers of the compounds **88** to **91**. This has made the determination of the degree of asymmetric transmission difficult, but it almost certainly is more than 90 percent.

Asymmetric transfer has also been demonstrated for [2,3] sigmatropic rearrangements. A particularly interesting example involves the sulfonium salt **96** (*121*). This salt, which was optically active by virtue of having been resolved as the dibenzoyl hydrogen tartrate (*122*), upon treatment with base, rearranged to the sufide **97** in 94 percent enantimeric excess. Similar rearrangement of an achiral sulfonium salt with an optically active base in an optically active solvent gave product in up to 12 percent enantiomeric excess (*123*).

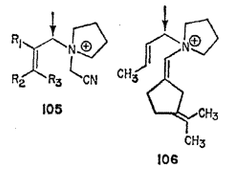


Wittig rearrangement of the benzyl ether **98** occurred suprafacially to give *trans* (83 percent) and *cis* (17 percent) alcohols **99** and **100** in 72 and 62 percent enantiomeric excess, respectively (*124*). The chiral amine oxide **101**, upon standing at −20°C, was converted to oxime ether **102**, with at least 85 percent transmission of asymmetry (*125*). Similar rearrangement of an amine oxide that is chiral at the nitrogen has been shown (*126*). The optically active benzene sulfenate **103** is reported (*127*), without details, to rearrange with inversion to the sulfone **104**.



The Lewis acid–catalyzed ene reaction of 1-pentene with menthyl glyoxalate gave product of up to 31 percent enantiomeric excess (*128*).

It is apparent that the transfer of asymmetry in sigmatropic processes is a general phenomenon and that a wide variety of such reactions should be of use in asymmetric synthesis. It is sufficient to point out only two such possibilities here. The salts **105** (*129*) (upon reaction with base) and **106**



(*130*) (upon heating) undergo [2,3] and [3,3] sigmatropic rearrangements, respectively. The latter reaction is probably highly stereoselective. Asymmetry of the salts could be introduced by a substituent at the points indicated (*131*). Another possibility, which to our knowledge has no reported parallel, is the use of a proline derivative in place of pyrrolidine.

Summary

Asymmetric synthesis is often the method of choice for obtaining chiral molecules. The use of one chiral molecule to create another can be effected in several ways. These vary in efficiency, depending on how the original chiral center or centers are used. In general, the least desirable reactions are those in which one chiral center is destroyed while another is created. Reactions in which the original reagent is recovered are better, and most efficient are those reactions in which the chiral reagent is used catalytically. Unfortunately, only a relatively few examples of this last class have been reported. Of these, the most effective and general reagents appear to be those that modify an olefinic bond.

References and Notes

1. J. D. Morrison and H. S. Mosher, *Asymmetric Organic Reactions* (Prentice-Hall, Englewood Cliffs, N.J., 1971).
2. The use of the term enantiomeric excess, rather than optical purity, is to be encouraged, since the latter is purely an operational term. See (*1*), p. 10, for a full discussion of this matter.
3. D. R. Boyd and M. A. McKervey, *Q. Rev.* **22**, 95 (1968); J. Mathieu and J. Weill-Raynal, *Bull. Soc. Chim. Fr.* (1968), p. 1211; H. J. Schneider and R. Haller, *Pharmazie* **28**, 417 (1973).
4. T. D. Inch, *Synthesis* (1970), p. 466.
5. G. Stork and S. R. Dowd, *J. Am. Chem. Soc.* **85**, 2178 (1963).
6. D. Meá-Jacheet and A. Horeau, *Bull. Soc. Chim. Fr.* (1968), p. 4571.
7. A. I. Meyers, G. Knaus, K. Kamata, *J. Am. Chem. Soc.* **96**, 268 (1974). We thank Prof. Meyers for communicating these results prior to publication.
8. K. Hiroi and S. Yamada, *Chem. Pharm. Bull. (Tokyo)* **21**, 54 (1973).
9. K. Hiroi, K. Achiwa, S. Yamada, *ibid.* **20**, 246 (1972).
10. S. Yamada, K. Hiroi, K. Achiwa, *Tetrahedron Lett.* (1969), p. 4233.
11. K. Hiroi and S. Yamada, *Chem. Pharm. Bull. (Tokyo)* **21**, 47 (1973).
12. S. Yamada and G. Otani, *Tetrahedron Lett.* (1969), p. 4237.
13. ———, *ibid.* (1971), p. 1133.
14. T. Igarishi, J. Oda, Y. Inouye, *Bull. Inst. Chem. Res. Kyoto Univ.* **50**, 222 (1972); *Chem. Abstr.* **77**, 164105d (1973).
15. R. J. Friary, Sr., J. M. Gilligan, R. P. Szajewski, K. J. Falci, R. W. Franck, *J. Org. Chem.* **38**, 3487 (1973).
16. S. Yamada, M. Shibasaki, S. Terashima, *Tetrahedron Lett.* (1973), p. 381.
17. S. Kumazawa, T. Kato, Y. Kitahara, *Chem. Lett.* (1973), p. 633; T. Kato, S. Kumazawa, Y. Kitahara, *Synthesis* (1972), p. 573.
18. L. A. Paquette, J. P. Freeman, S. Maiorana, *Tetrahedron* **27**, 2599 (1971); L. A. Paquette and J. P. Freeman, *J. Am. Chem. Soc.* **91**, 7548 (1969).
19. K. Igarishi, J. Oda, Y. Inouye, M. Ohno, *Agric. Biol. Chem.* **34**, 811 (1970).
20. For a related approach to this kind of compound, see R. Kuhn, H. E. Driesen, H. J. Haas, *Ann. Chem.* **718**, 78 (1968).
21. L. Marko and B. Heil, *Catal. Rev.* **8**, 269 (1973); J. D. Morrison, *Strem Chem.* **1**, 3 (1973).
22. T. Isoda, A. Ichikawa, T. Shimamoto, *Rika Gaku Kenkvusho Hokoku* **34**, 143 (1958); *Chem. Abstr.* **54**, 287f (1960).
23. Y. Izumi, *Angew. Chem. Int. Ed. Engl.* **10**, 871 (1971).
24. T. Ninomiya, *Bull. Chem. Soc. Jap.* **45**, 2545, 2548, 2551, 2555 (1972); E. I. Klabunovskii, N. P. Sokolova, A. A. Vedenyapin, Yu. M. Talanov, N. D. Subareva, V. P. Polyakova, N. V. Gorina, *Bull. Acad. Sci. U.S.S.R. Div. Chem. Sci.* **21**, 2306 (1972); T. Tanabe, K. Okuda, Y. Izumi, *Bull. Chem. Soc. Jap.* **46**, 514 (1973); Yu. I. Petrov, E. I. Klabunovskii, E. N. Lipgart, V. I. Neupokoev, *Katal. Reacts. Zhidk. Faze Tr. Vses. Konf. 3rd* (1971), pp. 254–263; *Chem. Abstr.* **79**, 17883u (1973); T. Yoshida and K. Harada, *Bull. Chem. Soc. Jap.* **44**, 1062 (1971); Y. Izumi and K. Ohkubo, *ibid.* p. 1330; F. Higashi, T. Ninomiya, Y. Izumi, *ibid.* p. 1333; T. Harada, M. Imaida, Y. Izumi, *ibid.*, p. 1419; Y. Izumi, S. Yajima, K. Okubo, K. K. Babievsky, *ibid.*, p. 1416; D. O. Hubbell and P. Rys, *Chimia* **24**, 442 (1970); T. Tanabe and Y. Izumi, *Bull. Chem. Soc. Jap.* **46**, 1550 (1973).
25. H. Poisel and U. Schmidt, *Chem. Ber.* **106**, 3408 (1973).
26. J-P. Vigneron, H. Kagan, A. Horeau, *Bull. Soc. Chim. Fr.* (1972), p. 3836.
27. H. Matsuo, H. Kobayashi, T. Tatsuno, *Chem. Pharm. Bull. (Tokyo)* **18**, 1693 (1970).
28. R. E. Harmon, S. K. Gupta, D. J. Brown, *Chem. Rev.* **73**, 21 (1973).
29. J. A. Osborn, F. H. Jardine, J. F. Young, G. Wilkinson, *J. Chem. Soc. (Lond.) Ser. A* (1966), p. 1711; S. Montelatici, A. van der Ent, J. A. Osborn, G. Wilkinson, *ibid.* (1968), p. 1054; B. R. James, *Homogeneous Hydrogenations* (Wiley, New York, 1973), pp. 198ff.
30. W. S. Knowles and M. J. Sabacky, *Chem. Commun.* (1968), p. 1445; ———, B. D. Vineyard, *ibid.* (1972), p. 10; *Ann. N.Y. Acad. Sci.* **172**, 232 (1972); W. S. Knowles and M. J. Sabacky, Belgian Patent 766,960 (1971); ———, B. D. Vineyard, German Patent 2,123,063 (1971); *Chem. Abstr.* **76**, P60074f (1972).
31. W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *Chem. Technol.* **2**, 590 (1972).
32. O. Korpiun, R. A. Lewis, J. Chickos, K. Mislow, *J. Am. Chem. Soc.* **90**, 4842 (1968); R. A. Lewis, O. Korpiun, K. Mislow, *ibid.*, p. 4847; J. P. Casey, R. A. Lewis, K. Mislow, *ibid.* **91**, 2789 (1969); R. A. Lewis and K. Mislow, *ibid.*, p. 7009; K. Naumann, G. Zon, K. Mislow, *ibid.*, p. 7012; G. Zon, K. E. DeBruin, K. Naumann, K. Mislow, *ibid.*, p. 7023.
33. H. Kagan and T. P. Dang, *Chem. Commun.* (1971), p. 481.
34. ———, *J. Am. Chem. Soc.* **94**, 6429 (1972).
35. J. D. Morrison, R. E. Burnett, A. M. Aguiar, C. J. Morrow, C. Phillips, *ibid.* **93**, 1301 (1971).

36. P. Abley and F. J. McQuillen, *J. Chem. Soc. (Lond.) Ser. C* (1971), p. 844; and references therein.
37. M. Čapka, P. Svoboda, M. Černý, J. Hetflejš, *Tetrahedron Lett.* (1971), p. 4787; R. H. Grubbs and L. C. Kroll, *J. Am. Chem. Soc.* **93**, 3062 (1971). For a review, see C. U. Pittman, Jr., and G. O. Evans, *Chem. Technol.* **3**, 560 (1973).
38. H. Pracejus and M. Bursian, East German Patent 92031 (1972).
39. J-C. Poulin, W. Dumont, T-P. Dang, H. Kagan, *C.R. Hebd. Seances Acad. Sci. Ser. C Sci. Chim.* **277**, 41 (1973); W. Dumont, J-C. Poulin, T-P. Dang, H. B. Kagan, *J. Am. Chem. Soc.* **95**, 8295 (1973).
40. B. Bogdanović, B. Henc, B. Meister, H. Pauling, G. Wilke, *Angew. Chem. Int. Ed. Engl.* **11**, 1023 (1972); B. Henc, thesis, Ruhr Universität Bochum (1971); B. Meister, thesis, Ruhr Universität Bochum (1971).
41. P. Pino, S. Pucci, F. Piacenti, G. Dell'Amico, *J. Chem. Soc. Ser. C* (1971), p. 1640.
42. I. Ogata and Y. Ikeda, *Chem. Lett.* (1972), p. 487; C. Botteghi, G. Consiglio, P. Pino, *Chimia* **26**, 141 (1972); M. Tanaka, Y. Watanabe, T. Mitsudo, K. Yamamoto, Y. Takegami, *Chem. Lett.* (1972), p. 483; C. Botteghi, L. Lardicci, R. Menicagli, *J. Org. Chem.* **38**, 2361 (1973); W. Himmele, H. Siegel, W. Aquila, F. J. Mueller, German Patent 2,132,414 (1973); *Chem. Abstr.* **78**, 97328 (1973); G. Consiglio, C. Botteghi, C. Salomon, P. Pino, *Angew. Chem.* **85**, 663 (1973).
43. B. Stern, A. Hirschauer, L. Sajus, *Tetrahedron Lett.* (1973), p. 3247.
44. C. Botteghi, G. Consiglio, P. Pino, *Chimia* **27**, 477 (1973).
45. B. M. Trost and T. J. Dietsche, *J. Am. Chem. Soc.* **95**, 8200 (1973).
46. G. Consiglio and C. Botteghi, *Helv. Chim. Acta* **56**, 460 (1973).
47. T. Aratani and S. Nakamura, German Patent 2,240,257 (1973); *Chem. Abstr.* **78**, 159,048d (1973).
48. H. Nozaki, H. Takaya, S. Moriuti, R. Noyori, *Tetrahedron* **24**, 3655 (1968); R. Noyori, H. Takaya, Y. Nakanisi, H. Nozaki, *Can. J. Chem.* **47**, 1242 (1969); I. S. Lishanskii, V. I. Pomerantsev, N. G. Illarionova, A. S. Khachaturov, T. I. Vakorina, *J. Org. Chem. U.S.S.R.* **7**, 1870 (1971).
49. Y. Kawakami and T. Tsuruta, *Tetrahedron Lett.* (1971), p. 1959; T. Tsuruta and Y. Kawakami, *Tetrahedron* **29**, 1173 (1973).
50. M. Guetté, J. Capillon, J-P. Guetté, *Tetrahedron* **29**, 3659 (1973); M. Guetté, J-P. Guetté, J. Capillon, *ibid.* **27**, 2863 (1971).
51. R. A. Kretchmer, *J. Org. Chem.* **37**, 2744 (1972).
52. W. E. Keyes and J. I. Legg, *J. Am. Chem. Soc.* **95**, 3431 (1973).
53. G. M. L. Cragg, *Organoboranes in Organic Synthesis* (Dekker, New York, 1973); H. C. Brown, *Boranes in Organic Chemistry* (Cornell Univ. Press, Ithaca, N.Y., 1972), pp. 285–287.
54. J. J. Partridge, N. K. Chadha, M. R. Uskoković, *J. Am. Chem. Soc.* **95**, 532 (1973).
55. ———, *ibid.*, p. 7171.
56. J. Fried, C. H. Lin, J. C. Sih, P. Dalven, G. F. Cooper, *ibid.* **94**, 4342 (1972); E. J. Corey and R. Noyori, *Tetrahedron Lett.* (1970), p. 311.
57. R. M. Carlson and A. H. Funk, *Tetrahedron Lett.* (1971), p. 3661; M. F. Grundon, D. Stewart, W. E. Watts, *Chem. Commun.* (1973), p. 573.
58. R. Bucourt, L. Nédélec, J-C. Gasc, J. Weill-Raynal, *Bull. Soc. Chim. Fr.* (1967), p. 561.
59. W. M. B. Könst, W. N. Speckamp, H. D. Houwen, H. O. Huisman, *Rec. Trav. Chim. Pays-Bas* **91**, 861 (1972).
60. R. Pappo, R. B. Garland, C. J. Jung, R. T. Nicholson, *Tetrahedron Lett.* (1973), p. 1827.
61. Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, in press; German Patent 2,102,623 (1971); *Chem. Abstr.* **76**, 59072 (1972).
62. U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **10**, 496 (1971).
63. R. A. Micheli, F. Bizzarro, N. Cohen, Z. G. Hajos, D. R. Parrish, L. A. Portland, W. Sciamanna, M. Scott, R. Vass, P. A. Wehrli, unpublished results; Z. G. Hajos and D. R. Parrish, *J. Org. Chem.* **38**, 3244 (1973).
64. S. Danishefsky, Lecture at Hoffmann-La Roche, Nutley, N.J., 13 November 1973.
65. G. Saucy, R. Borer, A. Fürst, *Helv. Chim. Acta* **54**, 2034 (1971).
66. G. Saucy and R. Borer, *ibid.*, p. 2121.
67. J. W. Scott, R. Borer, G. Saucy, *J. Org. Chem.* **37**, 1659 (1972); M. Rosenberger, A. J. Duggan, R. Borer, R. Müller, G. Saucy, *Helv. Chim. Acta* **55**, 2663 (1972); N. Cohen, B. Banner, R. Borer, R. Mueller, R. Yang, M. Rosenberger, G. Saucy, *J. Org. Chem.* **37**, 3385 (1972).
68. N. Cohen, B. L. Banner, J. F. Blount, M. Tsai, G. Saucy, *J. Org. Chem.* **38**, 3229 (1973).
69. Y. Kudo, M. Iwasawa, M. Kobayashi, Y. Senda, S. Mitsui, *Tetrahedron Lett.* (1972), p. 2125; S. Brandänge, S. Josephson, S. Vallén, *Acta Chem. Scand.* **27**, 1084 (1973); M. Kawana and S. Emoto, *Tetrahedron Lett.* (1972), p. 4855; R. Méric and J-P. Vigneron, *Bull. Soc. Chim. Fr. Ser. 2* (1973), p. 327; H. Cachier-Rivault and J-P. Vigneron, *ibid.* p. 2077; T. D. Inch, G. J. Lewis, G. L. Sainsbury, D. J. Sellers, *Tetrahedron Lett.* (1969), p. 3657; E. B. Dongala, D. L. Dull, C. Mioskowski, G. Solladié, *Tetrahedron Lett.* (1973), p. 4983; H. Nozaki, T. Aratani, T. Toraya, R. Noyori, *Tetrahedron* **27**, 905 (1971); H. J. Bestmann and L. Lienert, *Angew. Chem. Int. Ed. Engl.* **8**, 763 (1969); *Chem. Ztg. Chem. App.* **94**, 487 (1970); L. Hub and H. S. Mosher, *J. Org. Chem.* **35**, 3691 (1970); D. Cabaret, *C. R. Hebd. Seances Acad. Sci. Ser. C Chim.* **277**, 315 (1973).
70. A. Amariglio, H. Amariglio, X. Duval, *Bull. Soc. Chim. Fr.* (1969), pp. 1539, 1546; R. A. Auerbach and C. A. Kingsbury, *Tetrahedron* **29**, 1457 (1973); L. Salem, *J. Am. Chem. Soc.* **95**, 94 (1973); D. Nasipuri, C. K. Ghosh, P. R. Mukherjee, S. Venkataraman, *Tetrahedron Lett.* (1971), p. 1587; N. T. Anh, O. Eisenstein, J-M. Lefour, M-E. Trân Hun Dâu, *J. Am. Chem. Soc.* **95**, 6146 (1973).
71. For a review, see S. Yamada and K. Koga in *Selective Organic Transformations, Volume I*, B. S. Thyagarajan, Ed. (Wiley-Interscience, New York, 1970), pp. 1–33.
72. L. Lardicci, G. P. Giacomelli, R. Menicagli, *Tetrahedron Lett.* (1972), p. 687; R. A. Kretchmer, *J. Org. Chem.* **37**, 801 (1972); R. F. Borch and S. R. Levitan, *ibid.* **37**, 2347 (1972); O. Červinka and O. Kříž, *Collect. Czech. Chem. Commun.* **38**, 294 (1973); S. Yamaguchi and H. S. Mosher, *J. Org. Chem.* **38**, 1870 (1973); R. Andrisano, A. S. Angeloni, S. Marzocchi, *Tetrahedron* **29**, 913 (1973); R. Haller and H. J. Schneider, *Chem. Ber.* **106**, 1312 (1973); G. Giacomelli, R. Menicagli, L. Lardicci, *J. Org. Chem.* **38**, 2370 (1973); G. P. Giacomelli, R. Menicagli, L. Lardicci, *Tetrahedron Lett.* (1971), p. 4135; D. Nasipuri, C. K. Ghosh, R. J. L. Martin, *J. Org. Chem.* **35**, 657 (1970); C. J. Reich, G. R. Sullivan, H. S. Mosher, *Tetrahedron Lett.* (1973), p. 1505.
73. G. M. Giongo, F. DiGregorio, N. Palladino, W. Marconi, *Tetrahedron Lett.* (1973), p. 3195.
74. P. Bonvicini, A. Levi, G. Modena, G. Scorrano, *Chem. Commun.* (1972), p. 1188; M. Tanaka, Y. Watanabe, T. Mitsudo, H. Iwane, Y. Takegami, *Chem. Lett.* (1973), p. 239; C. J. Sih, J. B. Heather, G. P. Peruzzotti, P. Price, R. Sood, L.-F. H. Lee, *J. Am. Chem. Soc.* **95**, 1676 (1973); A. J. Solodar, German Patent 2,306,222 (1973); *Chem. Abstr.* **79**, 146,179 (1973).
75. Y. Ohgo, S. Takeuchi, J. Yoshimura, *Bull. Chem. Soc. Jap.* **44**, 583 (1971).
76. K. Yamamoto, T. Hayashi, M. Kumada, *J. Organometal. Chem.* **46**, C65 (1972); *J. Am. Chem. Soc.* **93**, 5301 (1971); K. Yamamoto, Y. Uramoto, M. Kumada, *J. Organometal. Chem.* **31**, C9 (1971); Y. Kiso, K. Yamamoto, K. Tamao, M. Kumada, *J. Am. Chem. Soc.* **94**, 4373 (1972); I. Ojima, T. Kogure, Y. Nagai, *Chem. Lett.* (1973), p. 541.
77. A. Nudelman, *Int. J. Sulfur Chem. Part B* **7**, 241 (1972); *ibid.* **6**, 1 (1971).
78. C. R. Johnson, R. A. Kirchoff, R. J. Reischer, G. F. Katekar, *J. Am. Chem. Soc.* **95**, 4287 (1973). The (*S*) compound was erroneously shown (C. R. Johnson, personal communication, 25 September 1973).
79. C. R. Johnson and C. W. Schroeck, *ibid.* **90**, 6852 (1968); **95**, 7418 (1973). We thank Professor Johnson for a preprint of this paper.
80. C. R. Johnson and J. P. Lockard, *Tetrahedron Lett.* (1971), p. 4589.
81. G. Tsuchihashi, S. Mitamura, K. Ogura, *ibid.* (1973), p. 2469; D. J. Abbott, S. Colonna, C. J. M. Stirling, *Chem. Commun.* (1971), p. 471; D. J. Abbott nad C. J. M. Stirling, *ibid.*, p. 472.
82. G. Tsuchihashi, S. Mitamura, S. Inoue, K. Ogura, *Tetrahedron Lett.* (1973), p. 323.
83. C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.* **93**, 5303 (1971); T. Durst, R. Viau, R. Van Den Elzen, and C. H. Nguyen, *Chem Commun.* (1971), p. 1334; T. Durst, R. Viau, M. R. McClory, *J. Am. Chem. Soc.* **93**, 3077 (1971).
84. G. Tsuchihashi, S. Iriuchijima, M. Ishibashi, *Tetrahedron Lett.* (1972), p. 4605.
85. G. Tsuchihashi, S. Iriuchijima, K. Maniwa, *ibid.* (1973), p. 3389.
86. For reviews, K. K. Babievskii and V. K. Latov, *Russ. Chem. Rev.* **38**, 456 (1969); see also (*1*, pp. 303–320) and (*4*).
87. E. Frainnet, P. Braquet, F. Moulines, *C. R. Hebd. Seances Acad. Sci. Ser. C Chim.* **272**, 1435 (1971); K. Harada and K. Matsumoto, *Bull. Chem. Soc. Jap.* **44**, 1068 (1971).
88. K. Harada, T. Iwasaki, T. Okawara, *Bull. Chem. Soc. Jap.* **46**, 1901 (1973); K. Harada and T. Yoshida, *J. Org. Chem.* **37**, 4366 (1972); *Chem. Commun.* (1970), p. 1071; *Bull. Chem. Soc. Jap.* **43**, 921 (1970).
89. K. Harada and J. Oh-Hashi, *Bull. Chem. Soc. Jap.* **43**, 960 (1970).
90. E. J. Corey, R. J. McCaully, H. S. Sachdev. *J. Am. Chem. Soc.* **92**, 2476 (1970).
91. E. J. Corey, H. S. Sachdev. J. Z. Gougoutas, W. Saenger, *J. Am. Chem. Soc.* **92**, 2488 (1970).
92. Homogeneous, nonasymmetric catalytic hydrogenations of the C=N bond have been achieved by McQuillen (*36*) with Rh-pyridine complexes. This method might be used to carry out asymmetric hydrogenations of this functional group. To our knowledge use of Rh $(P\phi_3)_3Cl$ or its derivatives to catalyze hydrogenation of C=N bonds has not been reported.
93. N. Langlois, T-P. Dang, H. B. Kagan, *Tetrahedron Lett.* (1973), p. 4865.
94. K. Harada and T. Okawara, *J. Org. Chem.* **38**, 707 (1973).
95. ———, K. Matsumoto, *Bull. Chem. Soc. Jap.* **46**, 1865 (1973).
96. M. S. Patel and M. Worsley, *Can. J. Chem.* **48**, 1881 (1970).
97. K. Harada and T. Okawara, *Bull. Chem. Soc. Jap.* **46**, 191 (1973).
98. U. E. Diner, M. Worsley, J. W. Lown, J-A. Forsythe, *Tetrahedron Lett.* (1972), p. 3145.
99. L. Neelakantan, *J. Org. Chem.* **36**, 2253 (1971).
100. K. Weinges, G. Graab, D. Nagel, B. Stemmle, *Chem. Ber.* **104**, 3594 (1971).
101. K. Weinges and B. Stemmle, *ibid.* **106**, 2291 (1973).
102. I. Ugi, *Intra-Sci. Chem. Rep.* **5**, 229 (1971).
103. D. Marquarding, P. Hoffmann, H. Heitzer, I. Ugi, *J. Am. Chem. Soc.* **92**, 1969 (1970).
104. G. W. Gokel, D. Marquarding, I. K. Ugi, *J. Org. Chem.* **37**, 3052 (1972).
105. L. F. Battelle, R. Bau, G. W. Gokel, R. T. Oyakawa, I. K. Ugi, *J. Am. Chem. Soc.* **95**, 482 (1973).
106. J-C. Fiaud and H. B. Kagan, *Tetrahedron Lett.* (1970), p. 1813.
107. ———, *ibid.* (1971), p. 1019.
108. J. Y. Chenard, D. Commereuc, Y. Chauvin, *Chem. Commun.* (1972), p. 750.
109. E. Frauendorfer, W. Steglich, F. Weygand, *Chem. Ber.* **106**, 1019 (1973); W. Steglish, E. Frauendorfer, F. Weygand, *ibid.* **104**, 687 (1971).
110. Y. Nogami, Y. Kawazoe, T. Taguchi, *Yakugaku Zasshi* **93**, 1058 (1973).
111. D. E. Nichols, C. F. Barfknecht, D. B. Rusterholz, F. Benington, R. B. Morin, *J. Med. Chem.* **16**, 480 (1973); O. Červinka and O. Kříž, *Z. Chem.* **12**, 135 (1972); L. Horner and D. H. Skaletz, *Tetrahedron Lett.* (1970), p. 3679; U. Busser and R. Haller, *ibid.* (1973), p. 231.
112. T. Yoshida and K. Harada, *Bull. Chem. Soc. Jap.* **45**, 3706 (1972); A. de Savignac, M. Bon, A. Lattes, *Bull. Soc. Chim. Fr.* (1972) p. 3426; J-P. Charles, H. Christol, G. Solladié, *ibid.* (1972), p. 1124; *ibid.* (1970), p. 4439.
113. L. Neelakantan, *J. Org. Chem.* **36**, 2256 (1971).
114. R. Kelly and V. VanRheenen, *Tetrahedron Lett.* (1973), p. 1709.
115. K. Mislow, *Introduction to Stereochemistry* (Benjamin, New York, 1966), p. 131.
116. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. T. Li, D. J. Faulkner, M. R. Peterson, *J. Am. Chem. Soc.* **92**, 741 (1970).
117. D. Felix, K. Gschwend-Steen, A. E. Wick, A. Eschenmoser, *Helv. Chim. Acta* **52**, 1030 (1969).

118. P. Vittorelli, T. Winkler, H-J. Hansen, H. Schmid, *ibid.* **51**, 1457 (1968).
119. R. K. Hill, R. Soman, S. Sawada, *J. Org. Chem.* **37**, 3737 (1972). Because of a typographical error, the (*R*)-acid is shown in the paper of Hill *et al.* We thank a referee of our article here for bringing this to our attention.
120. W. Sucrow, B. Schubert, W. Richter, M. Slopianka, *Chem. Ber.* **104**, 3689 (1971); W. Sucrow and W. Richter, *ibid.*, p. 3679; W. Sucrow and B. Girgensohn, *ibid.* **103**, 750 (1970); W. Sucrow, P. P. Caldeira, M. Slopianka, *ibid.* **106**, 2236 (1973); W. Sucrow and P. Polyzou, *Tetrahedron Lett.* (1971), p. 1833.
121. B. M. Trost and R. F. Hammen, *J. Am. Chem. Soc.* **95**, 963 (1973).
122. Because of the ability of the sulfonium salt to racemize by inversion, it is possible to convert all of the material to one optically pure salt.
123. B. M. Trost and W. G. Biddlecom, *J. Org. Chem.* **38**, 3438 (1973).
124. J. E. Baldwin and J. E. Patrick, *J. Am. Chem. Soc.* **93**, 3556 (1971).
125. Y. Yamamoto, J. Oda, Y. Inouye, *Chem. Commun.* (1973), p. 848.
126. M. Moriwaki, S. Sawada, Y. Inouye, *ibid.* (1970), p. 419.
127. S. Braverman, *Int. J. Sulfur Chem. Part C* **6**, 149 (1971).
128. O. Achmatowicz, Jr., and B. Szechner, *J. Org. Chem.* **37**, 964 (1972).
129. L. N. Mander and J. V. Turner, *ibid.* **38**, 2915 (1973).
130. P. M. McCurry, Jr., and R. K. Singh, *Tetrahedron Lett.* (1973), p. 3325.
131. The transfer of asymmetry for a structure closely related to **106** has been demonstrated: R. K. Hill and N. W. Gilman, *ibid.* (1967), p. 1421.

Iron and Susceptibility to Infectious Disease

In the resolution of the contest between invader and host, iron may be the critical determinant.

Eugene D. Weinberg

Precisely three decades have elapsed since Schade and Caroline described evidence for the presence of strong iron binding proteins in egg white and plasma, and suggested that the ligands might function to withhold the metal from bacterial invaders (*1*). At that time, it was known that a prompt and consistent host response to bacterial invasion is a reduction in the amount of iron in the blood plasma. The reduction is now understood to be brought about by suppression of intestinal assimilation of iron (*2*) and by an increase in the quantity of the metal stored in the liver (*3*). Inasmuch as successful invaders obviously obtain the iron that is essential for their growth from living tissues, the microbes must either have a mechanism that enables them to destroy host ligands or else have the potential to produce their own powerful iron binding compounds. No evidence exists for the former mechanism; but in 1952, Neilands and his students began to describe microbial metabolites that can vigorously extract iron from a variety of environments (*4*), and several laboratories have subsequently participated in the development of this field [for a review, see (*5*)].

Thus, by 1960, enough information was available for studies to be made of the confrontations between the iron chelators of hosts and those of microbial invaders. In the earliest study (*6*), on pasteurellosis, several principles were recognized that remain valid. Parenterally administered iron, which enhances the infectious process, has no effect on (i) mobilization or activity of phagocytic cells, (ii) antibody production or activity of complement, or (iii) toxicity of dead organisms. Within the past decade, numerous reports on the competition for iron between hosts and invaders have appeared (*7*, *8*), and there is general agreement that excess iron simply functions as a microbial nutrilite. The ability of the host to withhold iron from microbes is called "nutritional immunity" (*9*).

In this article, I review (i) the microbial need for and acquisition of iron, (ii) the offensive advantage provided to the invaders by hyperferremia and hypotransferrinemia, and (iii) the defensive advantage provided to hosts by hypoferremia. I conclude by discussing the extent to which nutritional immunity might have general applicability in host-parasite interactions.

The author is a professor in the Department of Microbiology, Indiana University, and in the medical sciences program at the School of Medicine, Indiana University, Bloomington 47401.

Microbial Acquisition of Iron

Similar quantities of iron are required for the growth of plant, animal, and microbial cells (*10*). Green algae, mouse L cells, and gram-negative bacteria need from 0.3 to 1.8 micromolar concentrations of iron; most gram-positive bacteria and fungi need from 0.4 to 4.0 μM iron. Minimal synthetic culture mediums contain from 0.5 to 3.0 μM iron, usually as a contaminant of the sugar and the phosphate salts; commonly used complex culture mediums contain 3.0 to 12.0 μM iron. Thus laboratory mediums generally need not be enriched with additional iron to support growth.

Nevertheless, because of the extreme insolubility of ferric iron at neutral *p*H, aerobic and facultative microbial cells must synthesize phenolates or hydroxamates to solubilize and assimilate the metal; compounds with these functions are called siderophores (*11*). Although anaerobic bacteria do not need to produce ferric iron binding compounds (because the metal is in the reduced valence state in their growth environments), they probably form transport ligands that have a selective affinity for ferrous iron (*11*). Those aerobic and facultative strains that are unable to synthesize siderophores (that is, are anautosequesteric) must, of course, be supplied with preformed phenolates or hydroxamates in addition to iron.

Although the production of siderophores is repressed by quantities of iron greater than those needed for growth, the repression is by no means absolute in iron-rich environments. The quantity of the nonrepressible residue of siderophores is actually much greater than that needed for growth of anautosequesteric mutants (*11*). In systems in vitro, it has been observed that autosequesterism is restricted by elevated temperatures (*12*); it is possible that the ability of invaders to synthesize iron ligands in the host is suppressed by fever (*13*).