TOPICS IN STEREOCHEMISTRY

VOLUME 18

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TOPICS IN

STEREOCHEMISTRY

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To the 1987 Nobel Laureates in Chemistry
Donald J. Cram, Jean-Marie Lehn
and
Charles J. Pedersen

INTRODUCTION TO THE SERIES

It is patently impossible for any individual to read enough of the journal literature so as to be aware of all significant developments that may impinge on his or her work, particularly in an area such as stereochemistry, which knows no topical boundaries. Stereochemical investigations may have relevance to an understanding of a wide range of phenomena and findings irrespective of their provenance. Because stereochemistry is important in many areas of chemistry, comprehensive reviews of high quality play a special role in educating and alerting the chemical community to new stereochemical developments.

The above considerations were reason enough for initiating a series such as this. In addition to updating information found in such standard monographs as *Stereochemistry of Carbon Compounds* (Eliel, McGraw-Hill, 1962) and *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965; reprinted by American Chemical Society, 1981) as well as others published more recently, the series is intended also to deal in greater detail with some of the topics summarized in such texts. It is for this reason that we have selected the title *Topics in Stereochemistry* for this series.

The series is intended for the advanced student, the teacher, and the active researcher. A background of the basic knowledge in the field of stereochemistry is assumed. Each chapter is written by an expert in the field and, hopefully, covers its subject in depth. We have tried to choose topics of fundamental importance aimed primarily at an audience of inorganic and organic chemists. Yet, many of these topics are concerned with basic principles of physical chemistry and some deal with stereochemical aspects of biochemistry as well.

It is our intention to produce future volumes at intervals of one to two years. The editors will welcome suggestions as to suitable topics.

We are fortunate in having been able to secure the help of an international board of editorial advisors who have been of great assistance by suggesting topics and authors for several chapters and by helping us avoid, in so far as possible, duplication of topics appearing in other, related monograph series. We are grateful to the editorial advisors for this assistance, but the editors and authors alone must assume the responsibility for any shortcomings of *Topics in Stereochemistry.*

E. L. ELIEL
S. H. WILEN

PREFACE

In the first chapter in this volume William A. Bonner surveys the fascinating research of scientists in several disciplines who have proposed hypotheses and carried out experiments aimed at understanding the origins of the chiral homogeneity of naturally occurring compounds. The stereochemical bias giving rise to so many enantiomerically pure compounds in nature is but one facet of the general question of the origin of life on earth. The range of experiments and techniques applied to the solution of this problem is very impressive. While there is not yet a definitive answer to the source of the enantiomeric bias, we believe that readers will be pleased to have the key facts and their interpretation as of 1987 presented and carefully reviewed by one of the principal participants in this multidisciplinary research effort.

The second chapter, by N. A. Porter and P. J. Krebs, deals with radical pair reactions. Both old and new stereochemical aspects of radical coupling are examined from the perspective of kinetics as well as that of coupling equilibria. In a short but far ranging analysis the authors describe the fate of radical pairs in solids and in other molecular aggregates (such as micelles) as well as in solution.

In the third chapter Henri Brunner examines enantioselective syntheses of organic compounds catalyzed by chiral transition metal compounds. In this survey Brunner has focused on quantitative results reported during the three-year period 1984–1986, during which a very large number of such syntheses have been reported. Much of the data presented is in the form of tables which are organized according to optically active catalyst ligands and reaction product structures. We believe that this collection of data will be of help to synthetic chemists, in particular, in the design of new stereoselective reactions.

The fourth and last chapter in this volume is a review of kinetic resolution by H. B. Kagan and J. C. Fiaud. This approach to optical activation, once considered limited to enzymatic reactions, has in recent years become a very practical way of preparing chiral compounds in nonracemic—even enantiomerically pure—form by purely chemical processes. This turn of events is in part due to recent developments leading to the very efficient kinetic resolution of compounds that can serve as starting materials and as intermediates in stereoselective syntheses of current interest. The seminal discovery by Barry Sharpless et al. (*J. Amer. Chem. Soc.*, **1981**, *103*, 6237) of asymmetric synthesis of optically active epoxides from allylic alcohols coupled with kinetic resolution of the unreacted chiral allylic alcohol, in particular, dramatized the possibilities of kinetic resolution. Remarkably, kinetic resolution has also been applied to the optical activation of compounds on a commercial scale. Another and very significant reason for the increased application of kinetic resolution methods is a better understanding of the theory of such processes, which the authors have pioneered in their research and which they review in this chapter.

We are pleased to dedicate this volume to the 1987 Nobel Laureates in Chemistry, Dr. Charles J. Pedersen (DuPont), Professor Donald J. Cram (UCLA), and Professor Jean-Marie Lehn (Strasbourg and Collège de France, Paris); we are proud to have Professor Lehn as one of the members of our Editorial Advisory Board. The 1987 Nobel Prize was awarded "for development and use of molecules with structure-specific interactions of high selectivity"; stereochemical selectivity has clearly played an important part in the work recognized by the Nobel Prize. One aspect of the work leading to the award was featured in the preceding volume of *Topics in Stereochemistry*: J. F. Stoddart, "Chiral Crown Ethers," **1987**, *17*, 207.

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January 1988

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TOPICS IN STEREOCHEMISTRY

VOLUME 18

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Origins of Chiral Homogeneity in Nature

WILLIAM A. BONNER

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I. INTRODUCTION

Molecules that have the structural possibility of existing as either of two enantiomers, a "right-handed" form or a mirror-image "left-handed" form, are said to be chiral (from the Greek *cheir*, meaning hand). Chiral molecules are *optically active*, that is, they have the ability to rotate the direction of polarization of plane polarized light, one enantiomer being *dextrorotatory* [(+) rotation] and the other *levorotatory* [(−) rotation]. Organic molecules associated in nature with living matter are usually chiral and, accordingly, since the time of Pasteur the optical activity of such chiral molecules has been recognized as one of the principal hallmarks of life. It is thus not surprising that measurable optical activity has been suggested recently as a prime criterion for the recognition of life elsewhere in the universe (1, 2). It has also been discovered that life's crucial biomolecules are not only optically active, but that each has its own unique and constant sense of chirality, which is characterized further by essentially complete enantiomeric homogeneity. Thus, as is well known, we find that L-amino acids (or *S*) are the unique monomer subunits of protein polymers, that D-ribose (related by stereochemical conventions to D-glyceraldehyde) (or *R*) and 2-deoxy-D-ribose are the monomer units of the RNA and DNA nucleic acid polymers, and that D-glucose is the exclusive monomer unit of glycogen and of the plant polysaccharide polymers, starch, and cellulose. The current biosphere is thus commonly characterized as being composed of L-amino acids and D-sugars. On the other hand, heterogeneity of chirality sense is tolerated and frequently observed among Nature's less consequential chiral molecules (e.g., certain terpenes) peripherally associated with living matter (3), and D-amino acids are found in rare instances involving proteins from bacterial cell walls and a few other sources (3, 4). Today it is generally accepted that enantiomeric homogeneity of the monomers making up the critical biopolymers is not only essential for the existence of life, but that self-replicating living matter would be impossible without such absolute enantiomeric purity (5). Fundamental questions thus arise as to the ultimate origin of the unique chirality senses of our biosphere. When, where, and by what mechanism(s) did they arise, and how did they achieve their absolute chiral homogeneity? Such questions, which have intrigued scientists since the time of Pasteur, have recently received increasingly widespread attention. A number of review articles addressing these questions has appeared in the past two decades, of which several are relatively comprehensive (3, 4, 6–9). Our intention in this chapter is to review critically the plethora of recent experimental, theoretical, and speculative publications pertaining to these questions, emphasizing the most recent literature to mid-1986.

II. BIOTIC THEORIES

Theories for the origin of a single chirality sense in Nature fall into two main categories, *biotic* and *abiotic.* Biotic theories presuppose that life on Earth originated at some advanced stage of chemical evolution from a primordial racemic environment, and that as living matter developed it somehow selected the utilization of today's L-amino acids and D-sugars as being the most efficient for continuous progression into higher forms. Such theories argue that the origin of chirality is an evolutionary process linked with the origin of life itself, and is an inevitable consequence of the evolution of living matter (10). In other words, chiral homogeneity developed as the molecular complexity of life itself developed, and the former was not a prerequisite of the latter. In 1957 Wald (11) suggested that the preferential incorporation of amino acids of one chirality into helical secondary structures of growing polypeptide chains might have been the original basis for chiral selection. Later theories postulate that D- and L-systems of organisms, unable to mate and frequently mutually antagonistic, arose on the racemic primitive Earth, and that eventually organisms of one chirality prevailed by the intervention of any one of a number of chance events. Such events include accidental changes in the environment favoring one system of organisms in their territorial competition (12), random mutations making one system inoperative (13), and random mutations allowing one system of organisms to develop a "killer enzyme" (e.g., a D-peptidase) which kills organisms of the enantiomeric system (14). Recently it has been suggested (15) that all life developed from a common ancestor which already had its chirality selected by the chance intervention of environmental stresses or by "stylistic differences" favoring a particular chirality. It has been argued that the presence of the enzyme D-amino acid oxidase in certain contemporary organisms (11), as well as the rare occurrence of D-amino acids in the cell walls of certain bacteria (13) and antibiotics (14), support the concept that organisms of a competing D-system existed on the primitive Earth.

Biotic theories are fundamentally speculative and imprecise as to mechanistic details, although a number are presented with elaborate mathematical analyses, which lend them notes of sophistication and authenticity. They are by nature not amenable to experimental verification, and are thus beyond testing in any meaningful scientific sense. A fundamental criticism of the proposition that living matter predated chiral homogeneity on the primitive Earth was advanced by Avetisov and co-workers (5) in 1985. Recent elegant experiments (16) involving the template-directed (matrix) oligomerizations of nucleotides have shown that the formation of chirally pure polynucleotides is substantially dependent on the chiral purity of the monomers. This leads to the conclusion (5) that only a chirally pure medium can sustain the existence and development of self-replicating systems, and that even the simplest of these can originate only in a medium already possessing a high degree of chiral purity. This means that the origin of self-replicating systems, on which life depends, could have occurred only *after* a previous "global" symmetry breaking in the racemic environment of the primitive Earth.

III. ABIOTIC THEORIES

Abiotic theories assume that the homochirality and stereospecific molecular interactions characteristic of the current biosphere could not have originated without some initial asymmetric bias (albeit small) in the primordial molecular environment, and accordingly seek to find abiotic mechanisms whereby such small asymmetries might have been engendered by external or internal factors in the racemic milieu, and then have been subsequently amplified to magnitudes useful for biotic evolution. In such a scenario, life at its origin *already had available* chiral molecules possessing an enantiomeric homogeneity sufficient to allow their stereoselective evolution into the chirally pure higher structures characteristic of our present biota. Abiotic theories have been the subject of intensive theoretical and experimental investigations over the past two decades, investigations which have produced a number of definitive answers regarding the mechanisms studied.

A. Chance Mechanisms

Abiotic theories, in turn, fall into two subcategories, *chance* and *determinate* mechanisms. Chance mechanisms presuppose physical processes for symmetry breaking at the molecular level (i.e., processes capable of producing a net enantiomeric excess) which have an equal probability of affording either enantiomer (D or L) from the racemic or prochiral environment. In any given molecular event initiated by the process, either D or L is selected randomly. Determinate mechanisms, assume that some intrinsic internal or environmentally external *chiral physical force* acts on the racemic or prochiral primordial molecular milieu in such a way as to cause production of a preponderance of one of the enantiomers (i.e., causing $[\mathrm{D}] \neq [\mathrm{L}]$). In either case, the randomly or deterministically selected small enantiomeric excess may then be amplified to a biotically useful magnitude by subsequent stereoselective mechanisms which we shall consider later. At this point we examine recent developments regarding both chance and determinate mechanisms.

1. Spontaneous Symmetry Breaking Models

If we flip a coin, it has a 50:50 chance of coming up heads (or tails). If we flip the coin 100 times, however, it does not necessarily come up 50 times heads and 50 times tails. It may be 54 heads and 46 tails, vice versa, or any other combination of positive numbers totaling 100. The deviation between the observed number of heads and that expected from chance is thought of as a "statistical fluctuation." When the number of flips is N, the expected number of heads will be $0.5 \times N$. As N becomes larger the statistical fluctuation becomes larger also, but the percentage fluctuation, that of (say) heads, relative to the expected, or the "relative statistical fluctuation," becomes smaller. Conversely, the smaller the number of flips, the larger will be the relative statistical fluctuation. The same is true of the random synthesis of D and L molecules from a prochiral precursor, or of allowing an exactly racemic mixture of D and L molecules to randomize by racemization. In all such cases we get a mixture that deviates from the "theoretical" 50:50 by a statistical fluctuation whose magnitude depends on the number of molecules (i.e., the number of "flips"). In 1932 Mills (17) calculated the mathematical probability of enantiomeric excesses arising by such statistical fluctuations. He showed that if 10^7 chiral molecules ($\approx 10^{-16}$ mol) were produced under random conditions, there was an even chance that the product would contain an excess of at least 0.021% of either enantiomer, and thus that it would be "practically impossible" to achieve a completely racemic product. Statistical fluctuations thus produce small and random enantiomeric excesses (defined as $([\text{D}]-[\text{L}])/([\text{D}]+[\text{L}])$, or $\%\text{D}-\%\text{L}$ in the mixture). Spontaneous symmetry breaking models, mathematical and experimental, owe their existence to these random enantiomeric excesses arising from statistical fluctuations.

In 1953 Frank (18) first proposed a "life model" consisting of a chemical substance that was a catalyst for its own production and an anticatalyst for production of its enantiomer. Developing the kinetic equations for growth of such mutually antagonistic self-reproducing systems, he showed that they were fundamentally unstable and led eventually to the dominance of one enantiomer. Sixteen years later and apparently unaware of Frank's work, Calvin (19) introduced the concept of "stereospecific autocatalysis" and showed diagrammatically (Figure 1) that chirally pure materials result inevitably in such systems. In Calvin's scheme we have two rapidly equili-

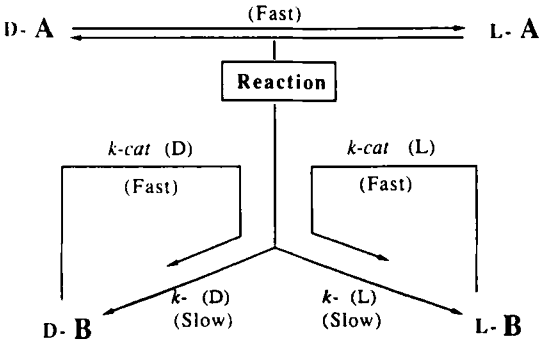


Figure 1. Stereospecific autocatalysis.

brating D and L enantiomers of reactant **A**, each of which is converted by some reaction into the corresponding enantiomers of product **B** at rates *k*(D) and *k*(L), which are slow. Product D-**B** can then act as a stereospecific autocatalyst for the formation of more D-**B** from D-**A**, and product L-**B** similarly catalyzes the formation of more L-**B**, each catalytic reaction proceeding at a much faster rate than the noncatalytic reaction (i.e., *k-cat*(D or L) $\gg$ *k*(D or L)). Owing to statistical fluctuations, however, the enantiomeric reactants D-**A** and L-**A** will not be present in exactly equal amounts at the outset. If D-**A** is in slight excess, for example, it will form a slight excess of its product D-**B**, which will rapidly catalyze formation of more D-**B**. Because of the rapid equilibration of the reactants D-**A** and L-**A** and the slowness of the uncatalyzed reaction rates, the system will thus rapidly become entirely product D-**B**. In 1971 Seelig (20), unaware of either Frank's or Calvin's ideas, independently proposed a third system including autocatalytic reactions with similar feedback loops, and showed by a computer simulation that tiny asymmetries in the initial concentrations of reactants will flip the entire system into one enantiomeric state.

Following the publications of Frank, Calvin, and Seelig, a number of papers have appeared by several authors who have developed a variety of additional stochastic models for spontaneous symmetry breaking and evolution into chirally homogeneous states (21–24, 273). These mathematical models, essentially more sophisticated versions of the ideas presented above, are generally based on the kinetic behavior of hypothetical racemic systems that are inherently unstable and undergo symmetry breaking at some random "bifurcation point," then rush inevitably into a state of chiral purity. None of these models rests on any experimental basis (except possibly those suggesting spontaneous resolution by crystallization, discussed below), and very few of the authors even suggest experiments which might test or support their models. The papers are generally replete with sophisticated kinetic equations and tend to be mathematically formidable for the nonspecialist, except for the lucid hydrodynamic analog of Buvet (25), which was developed because of this. It might be pointed out that the biotic theories discussed in Sect. II are additional examples of such symmetry breaking hypotheses, with spontaneous bifurcation occurring, however, only after life began.

Several authors recently presented convincing arguments against models wherein a small initial asymmetry resulting from statistical fluctuations is amplified into an eventual enantiomeric predominance. Czege and Fajszi (26) have developed a model, again assuming plausible starting conditions, in which small initial asymmetries in the system not only fail to amplify, but actually vanish. That two similar mathematical models with slightly different assumptions should lead to totally contradictory conclusions thus makes it questionable whether the earlier models have any relevance whatsoever for the origin of enantiomeric homogeneity. However, a number of actual experimental models for spontaneous symmetry breaking do in fact afford enantiomerically homogeneous chiral systems. They are examined in the following sections.

2. *Spontaneous Symmetry Breaking on Crystallization*

Racemic solids may crystallize from supersaturated solutions either as *racemic compounds* or as *conglomerates.* The more common racemic compounds contain an equal number of molecules of each enantiomer in the lattice of each crystal. The less common conglomerates consist of a mixture of crystals, which has an equal number of separate crystals of each enantiomer. The optical resolution of racemic compounds requires diastereomeric interactions, such as the use of resolving agents or chromatography on chiral phases. The resolution of conglomerates is more interesting both practically and prebiotically, since it can occur spontaneously during simple crystallization. If the resulting crystals are hemihedral and show left- and right-handed morphological characteristics, they are visually distinguishable and can be separated manually. This rare phenomenon allowed Pasteur in 1848 to perform the first optical resolution, that of racemic sodium ammonium tartrate, which crystallizes as a conglomerate below, and as a racemic compound above, a transition temperature of 27.2°C. The separate crystals of most conglomerates, however, are usually morphologically indistinguishable.

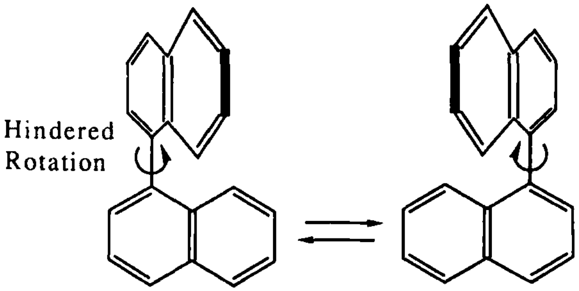
When a supersaturated solution of a racemic conglomerate is allowed to stand, it frequently deposits crystals of only one of its enantiomers. These can be separated carefully from the mother liquors, and an optical resolution thus achieved. The process is a random one, however, and in a duplicate experiment the other enantiomer may equally well be deposited (3). However, the crystallization of one desired enantiomer from a conglomerate solution may usually be guaranteed by consciously "seeding" the solution with a crystal of the desired enantiomer. This technique has proved important for resolving a number of optically active compounds commercially (27, 28), and many ingenious experimental modifications of the seeding technique have been developed to augment the efficiency of the process (28).

Though rare compared to racemic compounds, which comprise over 90% of all racemates (29), the number of known conglomerates is nevertheless impressive. By 1981 Jacques et al. (30) had compiled an inventory of nearly 250 conglomerates, conveniently listing their melting points, structural formulas, the means by which they were characterized, and literature citations. The list includes random organic racemates containing from 1 to 38 carbon atoms (71%), salts and complexes of amino acids and their derivatives (18%), miscellaneous salts of organic acids and bases (6%), and organometallic or inorganic complexes (5%). Their thorough and scholarly treatise (30) should be consulted for information on all pertinent theoretical, experimental, and practical aspects of phenomena involving racemates and their means of resolution. Since completion of this inventory several additional examples of spontaneous resolution have been reported (31), including many new octahedral complexes of cobalt with bidentate ligands (32).

Spontaneous resolution by crystallization was early championed (3) as a likely mechanism for the origin of optical activity in nature, and such suggestions are still current (33). It remains today without question the most effective means of chiral symmetry breaking, and is the most economical route for preparing pure enantiomers on scales ranging from a few grams to tons (30).

3. *"Total" Spontaneous Resolution*

Spontaneous resolution during the crystallization of certain conglomerates, as discussed above, produces in a single operation at best less than 50% of the total material in the original racemate. However, if the uncrystallized enantiomers remaining in solution could rapidly equilibrate while the slower crystallization of one enantiomer was occurring, the *entire* racemate would obviously crystallize eventually as a single enantiomer. Such a process, recently called "total spontaneous resolution" (28), would clearly provide an example of Calvin's "stereospecific autocatalysis" model (19) for complete chiral symmetry breaking. Several such "total" spontaneous resolutions have been observed experimentally.



R(-)-**1** S(+)-**1**

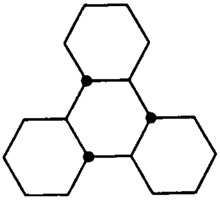
Figure 2. Enantiomers of 1,1′-binaphthyl (**1**).

Because of steric hindrance, 1,1′-binaphthyl (**1**) is subject to moderately restricted intramolecular rotation about its 1,1′-bond, and accordingly can exist as two enantiomers (Figure 2). These have specific rotations of (±)-245°, and half-lives for racemization in solution of *ca.* 15 min at 50°C. Racemic **1** may exist as a metastable low-melting (145°C) polymorph or a stable high-melting (159°C) polymorph. In 1971 Pincock and Wilson (34) discovered that racemic **1** underwent spontaneous resolution under three sets of conditions: (1) on allowing its supercooled melt to crystallize as the high-melting form; (2) on slowly heating the low-melting form to 145°C, where it melts to a metastable liquid which crystallizes as the high-melting form; and (3) on slowly heating the low-melting form to almost 145°C, where it undergoes a solid-state transformation to the stable high-melting form. In each case the high-melting form obtained was optically active, showing variable (+) and (−) optical rotations, and the analogy to Calvin's autocatalysis model was pointed out (34, 35).

A statistical study was then made (35) of the incidence and magnitude of the spontaneous optical activity produced. In 200 samples of spontaneously resolved **1** the specific rotations ranged from −218 to +206°, with the largest number having low rotations (±2 to ±48°). The observed rotations fitted a Gaussian distribution curve, with a mean of +0.18±86.4°. Thus nucleation of the enantiomers of **1** was a random process, giving a symmetrical distribution of (+) and (−) rotations and a mean of ≈0.0°. Subsequent studies were conducted (35, 36) to assess the effect of optically active impurities on the random nucleation of pure **1**. Some 18 different contaminants (including D and L pairs) were studied at various concentrations up to 30% by weight. Some impurities showed no effect, while others imparted an asymmetric bias to the spontaneous resolution of **1**. D- and L-mandelic acid gave comparable opposite effects, while other D and L pairs gave the same effect, suggesting that unknown contaminants of overriding power might be present and influencing the results. Pincock and co-workers later investigated the solid-state resolution of **1** mechanistically (37), as well as the spontaneous resolution of 4,4′-dimethyl-1,1′-binaphthyl (38) and the solid-state resolution and racemization of 4,4′-diamino-1,1′-binaphthyl (39). Earlier examples of "total" spontaneous resolutions are those of *N*-methyl-*N*-ethyl-*N*-allylanilinium iodide (3) and tri-*o*-thymotide (3, 40). Each is obtained in optically active form by slow crystallization from a solution which remains virtually racemic.

4. *Lattice-Controlled Reactions in Chiral Crystals*

The first instance of a chiral crystal lattice directing an asymmetric synthesis to yield an optically active product was reported by Farina and co-workers in 1967 (41). All-*trans* perhydrotriphenylene (**2**) has no alternating axis of symmetry, and can be resolved into its enantiomers. Racemic **2** forms an inclusion compound with *trans*-1,3-pentadiene (**3**), which on irradiation in the solid state with γ rays affords an isotactic polymer of *trans*-1,3-pentadiene (**4**). When an inclusion compound was prepared from **3** and *R*(−)-**2**, then irradiated, the polymer **4** showed an unambiguous (+) optical rotation, opposite to that of *R*(−)-**2**. An opposite effect was obtained using *S*(+)-**2**. Thus optical activity was produced under "rather primitive and scarcely



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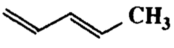

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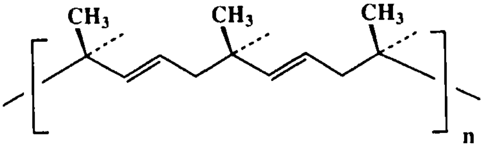

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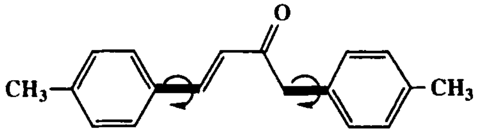
selective conditions." Similar results were obtained on γ irradiation of inclusion compounds of *cis*- or *trans*-**3** with deoxycholic acid (41).

Shortly thereafter, Penzien and Schmidt (42) provided a second example of a lattice-controlled solid state asymmetric synthesis. 4,4′-Dimethylchalcone (**5**) crystallizes as enantiomeric crystals. When individual monocrystals were exposed to bromine vapor, an optically active dibromo product (**6**) was obtained having a maximum, $[\alpha]_D^{28} = +9.8°$, corresponding to an optical yield of 6%. Products of either sign of rotation were noted.



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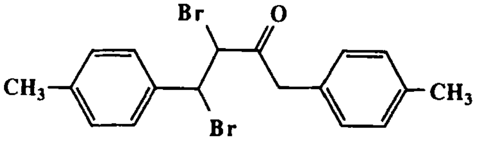
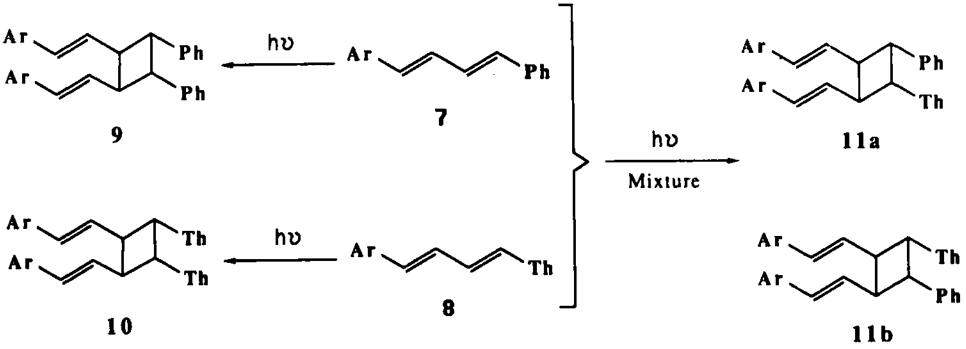


6

In 1974 Green and Heller (43) reinvestigated the bromination of **5**. In solution or in the melt, rotation about the emphasized single bonds in **5** cause rapid interconversion between right- and left-handed enantiomeric conformations. In the crystals, however, the conformations are frozen, and cannot interconvert. Also, in the chiral crystals of **5**, all molecules in any single crystal have the same conformation. Since polycrystalline samples of **5** contain both crystal chiralities in random proportions, the optical rotation of dibromide **6** was found to vary randomly in both sign and magnitude. However, when **5** was crystallized along with 3.97 mol % of optically active dibromide (+)-**6**, bromination of the mixture afforded only the (−)-**6** product. Opposite results were noted using 3.97 mol % (−)-**6**, only the (+)-**6** product now being obtained. Thus a small amount of the chiral product **6** induced crystallization of **5** in such a way as to produce exclusively **6** of the opposite chirality sense. Ignoring this observed "inversion effect" (Sect. IV-C), the authors then proposed the following autocatalytic mechanism for the origin of homochirality. A racemic material whose enantiomers interconvert in the liquid state crystallizes into a chiral crystal structure, which undergoes a solid-state reaction to give a chiral product. The product, nonracemizable in the liquid state, then induces further crystallization of the reactant into that crystal chirality which yields more product of the same chirality.

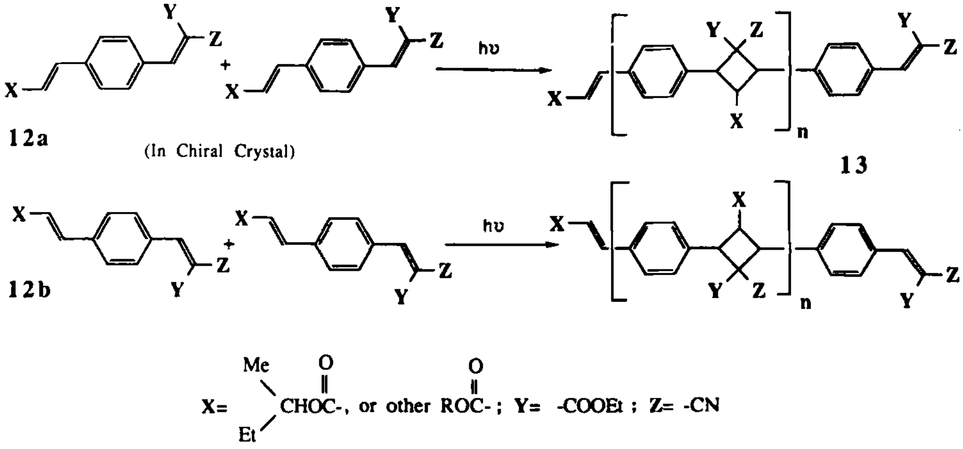
Another novel lattice-controlled asymmetric synthesis involves a $[2\pi + 2\pi]$ photocycloaddition reaction within a two-component single crystal made up of two 1,4-diarylbutadienes (44). The 1,4-diaryl-1,3-butadienes **7** and **8** undergo solid-state photocycloadditions to form the dimers **9** and **10**, respectively (Figure 3). Compounds **7** and **8** are isomorphous, and when their 1 : 1 mixture is cooled from a melt or crystallized from ethanol, mixed crystals are formed. On irradiating a polycrystalline sample of such mixed crystals (using appropriate filters such that the formation of the homodimers **9** and **10** are minimized), the racemic mixed dimer **11a,b** results. A large *single* mixed crystal containing 85% **7** and 15% **8** was then prepared, powdered, and irradiated. The resulting dimer **11** was consistently optically active, with $[\alpha]_D$ randomly $\sim \pm 1.0°$.



Ar = 2,6-Dichlorophenyl; Th = Thienyl

Figure 3. Asymmetric photodimerization of 1,4-diarylbutadienes.

In 1975 Addadi and co-workers, again using $[2\pi + 2\pi]$ topochemical photocycloadditions, reported (45) the first asymmetric synthesis of chiral dimers and polymers by a lattice-controlled reaction in a *one-component* chiral crystal, and the first such synthesis in a crystal of racemic composition. An optically pure polycrystalline sample of the divinyl monomer **12**, having a chiral *s*-butyl group in one of its vinyl sidechains, was irradiated ($\lambda > 300$ nm) to give a dimer plus low- and higher-molecular-weight polymers (**13**) which were separable by chromatography (Figure 4). The dimer and low-molecular-weight polymer were optically active, with rotations *opposite* in sign to that of the starting monomer **12**. That this asymmetric synthesis was not due to the chirality of the *s*-butyl groups in the monomer was shown as follows.



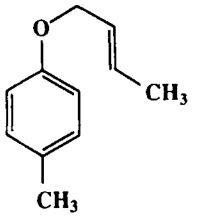
$$X = \overset{Me}{\underset{Et}{}}\!\!>\!CH\overset{O}{\overset{\|}{C}}O\text{-, or other } RO\overset{O}{\overset{\|}{C}}\text{-} ;\ Y = \text{-COOEt} ;\ Z = \text{-CN}$$

Figure 4. Asymmetric polymerization in enantiomeric monomer crystals.

Racemic **12** does not spontaneously resolve on crystallization, but gives a solid solution of the two enantiomers. With its chiral handles (X) randomly arranged, each enantiomeric single crystal of racemic **12** has equal numbers of Xs of opposite chirality, and each enantiomer has an equal probability of crystallizing. A large crystal of racemic **12**, which was optically inactive in solution, gave on irradiation a mixture of products having $[\alpha]_D^{25} = -24°$. Thus the dimer and polymer products owed their optical activity to the backbone configuration of the crystal lattice of the racemic monomer. It was subsequently shown that the irradiation of optically pure (*S*)-(+)-**12** or (*R*)-(−)-**12** crystals also led to chiral dimers, trimers, and oligomers in quantitative (>97%) enantiomeric yield (46). Extension of such studies to include *achiral* monomers similar to **12** (X = *i*-Pr, 3-pentyl) again led to polymers of high optical purity (47). Solid-state photodimerization reactions have also been used ingeniously for the enantiomeric purification of several 1-arylethanols (48). The principles behind such topochemical reactions in the crystalline state have been reviewed extensively (49). Later attempts by Addadi and co-workers to use their photodimerization–polymerization reactions in an autocatalysis scheme which might be a model for the origin of chirality are described in Sect. IV-C.

5. *Reactions in Cholesteric Phases*

In 1975 Saeva and co-workers (51) first described a "lattice-controlled" reaction using, instead of chiral crystals, the *anisotropic* ordering of a solute in a liquid crystal mesophase, which then directed an asymmetric synthesis not possible in an isotropic medium. In a cholesteric mesophase there exists a "superchiral" environment, with a macroscopic helical structure formed by the chiral organization of "nematic-like" layers having uniaxial molecular rearrangement within the layers. It was expected that this ordering might induce an achiral solute in the mesophase to react asymmetrically. The authors conducted a Claisen rearrangement of γ-methallyl-*p*-tolyl ether (**14**) at 200°C in a mesophase formed from a mixture of 5% **14** in 95% cholesteryl *p*-nitrobenzoate. The 2-(α-methallyl)-4-methylphenol product (**15**) was shown



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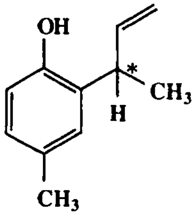
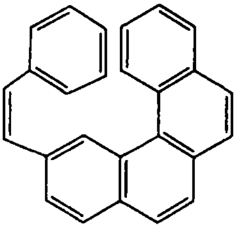


15

by its circular dichroism to be optically active, but no optical yield was reported. The effect was not observed with 30% of **14** in the mixture, indicating that the chirality of the cholesteryl *p*-nitrobenzoate itself was not responsible for the asymmetric effect observed.

A second example was provided 3 years later by Nakazaki and co-workers (52), who irradiated a mixture of 1% by weight of 2-styrylbenzo[c]phenanthrene (**16**) and a trace of iodine in a mesophase consisting of a 3 : 2 mixture of cholesteryl nonanoate and cholesteryl chloride, using ultraviolet light at



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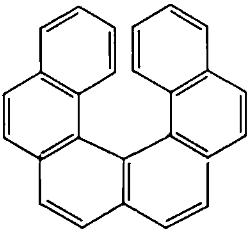
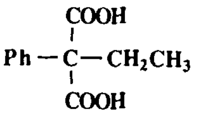


17

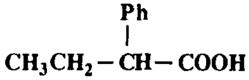
23°C. The hexahelicene (**17**) product obtained had $[\alpha]_{\mathrm{D}}^{23}$ +40°, corresponding to an optical yield of 1.1%. When the photocyclization was conducted at 55–60°C, slightly above the cholesteric–isotropic liquid transition temperature, the product was optically inactive, suggesting that the macrostructural chirality of the mesophase was responsible for the asymmetric synthesis. Similar results were obtained with a cholesteryl benzoate liquid crystal at 145–150°C, and with other cholesteric mesophases (212).

Several additional examples of asymmetric transformations occurring in cholesteric liquid crystals were subsequently reported. These include the decarboxylation of ethylphenylmalonic acid (**18**) in cholesteryl benzoate at 160°C to obtain *R*(−)-2-phenylbutanoic acid (**19**) ($[\alpha]_D^{27} = -14.2°$; 18% e.e.) (53), the transformation of a racemic mixture of sulfoxide enantiomers into mixtures with one enantiomer in up to 9.2% excess (54), and the Hofmann elimination pyrolysis of trimethylcyclooctylammonium hydroxide (**20**) in several new mesophases, to yield *R*(−)-*trans*-cyclooctene (**21**) in up to 7.2% e.e. (55).



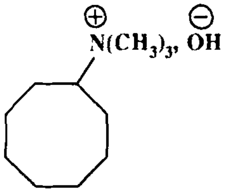
$$Ph-\overset{COOH}{\underset{COOH}{C}}-CH_2CH_3$$

18



$$CH_3CH_2-\overset{Ph}{CH}-COOH$$

19



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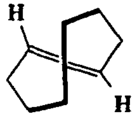

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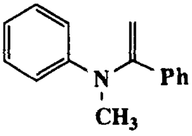
In 1979 Eskenazi et al. (56) attempted the photocyclizations of α-(*N*-methylanilino)styrene (**22**) to *N*-methyl-2-phenylindoline (**23**) and of the nitrone **24** to the oxaziridine **25** in a number of cholesteric mesophases. Since the products **23** and **25** proved to be optically inactive, an attempt was made



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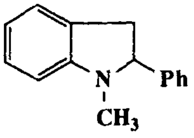

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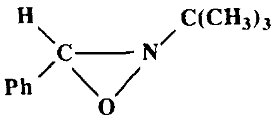

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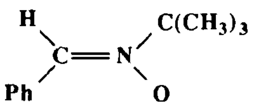


25

to duplicate the earlier claims of successful asymmetric conversions involving **14** (51), sulfoxides (54), and **18** (53). In no case was any significant optical activity observed in the products obtained. The authors concluded that the previously reported high optical rotations in these experiments were probably due to contamination of the isolated products with residual cholesteric material, and that "the effect of mesomorphic anisotropic ordering on asymmetric induction remains to be clearly established."

6. *Asymmetric Adsorption on Quartz*

The silica mineral quartz is frequently found in nature in well-defined crystals having either a right- or left-handed morphological handedness, and an optical rotation of $(\pm)21.72^\circ\ \text{mm}^{-1}$ along the optical axis for 589-nm light. As early as 1938, Karagounis and Coumoulos, after reporting the partial resolution of a racemic chromium complex by adsorption on optically active quartz crystals, suggested that such adsorption of racemates by chiral inorganic minerals might have constituted a mechanism for the origin of optical activity in nature, a view later championed by Bernal (3). In 1938, however, Amariglio and co-workers were completely unsuccessful in their attempts to repeat the dozen or so earlier reports in the literature describing resolutions on chiral quartz crystals, and accordingly concluded that the earlier positive findings were erroneous and due to one or more of several artifacts involving the polarimetric observation techniques employed (57). Thus in the early 1970s the validity of the phenomenon of asymmetric adsorption on chiral minerals was an open question, as was its possible relevance in primordial chiral symmetry breaking.

This ambiguity was addressed in 1974 by Bonner and co-workers (58), who used a method not relying on the polarimetric observation of optical rotation to assess the possible occurrence of asymmetric adsorption. The alternative technique, which involved the use of radioisotopically labeled substrates, was designed to circumvent the artifacts enumerated by Amariglio (57). The radioactivities of very dilute ($2 \times 10^{-5}\ M$) solutions of ^{14}C- and ^{3}H-labelled D- and L-alanine hydrochlorides in anhydrous dimethylformamide were measured before and after equilibration with finely powdered *d*- and *l*-quartz under scrupulously anhydrous conditions. The difference in radioactivity count before and after equilibration then gave a direct measure of the total amount of labeled alanine adsorbed, and the difference in the fraction of D- and L-alanine adsorbed gave an indication of the asymmetric bias in the adsorption process. In 10 independent replicate experiments, the total adsorption of alanine by the quartz was some 20–30%, and *l*-quartz preferentially adsorbed L-alanine and *d*-quartz D-alanine, the "differential adsorption" ranging from 1.0 to 1.8%. These observations were later confir-

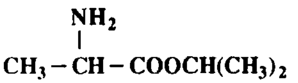
Table 1
Asymmetric Adsorption of DL-Alanine Hydrochloride by *d*- and *l*-Quartz

	Labeled Enantiomer in Racemate	
	D	L
1. Stock solution (counts)	82570	172626
2. Supernatant over *l*-quartz (counts)	64976	133185
3. Supernatant over *d*-quartz (counts)	60250	146477
4. % Adsorbed by *l*-quartz[a]	21.3	22.8
5. % Adsorbed by *d*-quartz[b]	27.0	15.1
6. Total racemate adsorbed (%)[c]	48.3	37.9
7. Differential adsorption (%)[d]	−11.8	20.3

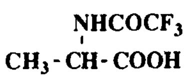
[a] 100 × (No. 1–No. 2)/No. 1.
[b] 100 × (No. 1–No. 3)/No. 1.
[c] No. 4 + No. 5.
[d] 100 × No. 4/No. 6–100 × No. 5/No. 6.

med using an artificially prepared D,L-alanine hydrochloride sample, with a ^{14}C label on the D- and a ^{3}H label on the L-alanine enantiomer, which could be counted separately. As illustrated in Table 1, the total DL-alanine adsorbed in these experiments was 38–48%, and the differential adsorption [defined as (% adsorbed on *d*-quartz − % adsorbed on *l*-quartz)/total adsorbed] was 11.8–20.3%. Moisture in the system led to a lack of adsorption or to nonreproducible results. The studies described above constituted the first unambiguous demonstration that *d*- and *l*-quartz actually do show asymmetric adsorption, and in fact do so with a "prebiotically realistic" substrate.

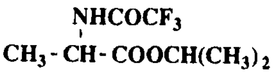
Kavasmaneck and Bonner (59) later investigated the quartz asymmetric adsorption phenomenon for its mechanistic details, using other amino acids and other amino acid derivatives. The isopropyl ester (**26**), the *N*-trifluoroacetyl (*N*-TFA) derivative (**27**), and the *N*-TFA isopropyl ester derivative (**28**) of


$$CH_3-\overset{NH_2}{\overset{|}{C}H}-COOCH(CH_3)_2$$

26


$$CH_3-\overset{NHCOCF_3}{\overset{|}{C}H}-COOH$$

27

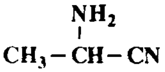

$$CH_3-\overset{NHCOCF_3}{\overset{|}{C}H}-COOCH(CH_3)_2$$

28

^{3}H-labeled DL-alanine were prepared, thus successively blocking the COOH, the NH_2, and both functional groups of the DL-alanine. The adsorption of these derivatives from dichloromethane solution was 90.2, 16.9, and 0.0%, respectively, showing that the NH_2 (or NH_3^+) group of the alanine was primarily responsible for its adsorption by quartz. The effectiveness of quartz in adsorbing *n*-butyl ester hydrochlorides of a number of amino acids from anhydrous dichloromethane was found to be greatest for basic (Lys, Try), less for an OH-containing neutral (Thr), still less for neutral amino acids (Ala, Val, Leu, Pro, Phe), and least for acidic amino acids (Glu, Asp). Within each class the extent of adsorption was influenced by the size of the molecule, varying inversely with molecular weight. Adsorption of **26** by quartz was found to be greatest in nonpolar solvents, and to diminish as solvent polarity increased. Finally, the asymmetric adsorption of D,L-alanine isopropyl ester (D,L-**26**) in chloroform was studied by fractional elution from *d*- and *l*-quartz, using gas chromatography (Sect. III-B-2-a) to estimate enantiomeric enrichment. Here *l*-quartz preferentially adsorbed D-**26** and *d*-quartz L-**26**, the enantiomeric enrichment among the various eluates ranging from 1.5 to 12.4%. The preference of *l*-quartz for D-**26** and *d*-quartz for L-**26** in chloroform was the reverse of that noted for unesterified D- and L-alanine in dimethylformamide, indicating that the nature of the functional groups (and perhaps the solvent) was important in determining the sign of the enantiomeric enrichment.

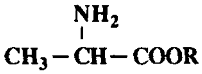
The asymmetric adsorption of alanine by *d*- and *l*-quartz was subsequently confirmed independently by other investigators using a slightly different system. Furuyama and co-workers (60) studied the adsorption of alanine enantiomers (and their hydrochlorides) by *d*- and *l*-quartz from very dilute solutions in anhydrous ethanol at −80°C, estimating the extents of adsorption by "^{14}C-tracer ninhydrin colorimetry." Again, *l*-quartz was found preferentially to adsorb L-alanine and *d*-quartz D-alanine, with asymmetric adsorption ranging from 1.2 to 2.0%. Since the concentration of ethanol solvent in these experiments was some 10^6 times larger than that of the alanine solute, it is clear that the adsorption affinity of quartz for alanine is much larger than that for ethanol. The addition of water to the system diminished the adsorption of alanine almost linearly, and at 20% water concentration, adsorption was negligible.

Another substrate of prebiotic relevance, which has been reported (61) capable of separation by asymmetric adsorption on quartz, is DL-α-aminopropionitrile (**29**). The sulfate salt of **29** in aqueous solution was exposed to *d*-quartz of various mesh sizes for 1 hr at 0°C or 24 hr at 15°C. The quartz was rinsed and the **29** remaining adsorbed was extracted with 10 *M* HCl in methanol, then was converted into its methyl ester (**30**, R = Me). The latter was transesterified with (+)-2-butanol/HCl to give the (+)-*s*-butyl ester



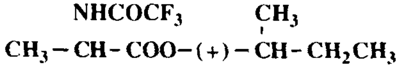
$CH_3-\overset{NH_2}{\overset{|}{C}H}-CN$

29



$CH_3-\overset{NH_2}{\overset{|}{C}H}-COOR$

30



$CH_3-\overset{NHCOCF_3}{CH}-COO-(+)-\overset{CH_3}{\overset{|}{C}H}-CH_2CH_3$

31

[**30**, $R = (+)$-*s*-Bu], which was finally converted to its *N*-TFA derivative (**31**). The D-Ala-(+)-*s*-Bu and L-Ala-(+)-*s*-Bu diastereomers of **31** can be separated and quantitatively analyzed by gas chromatography (Sect. III-B-2-a), thus providing an estimate of the enantiomeric composition of the original mixture of **29** antipodes adsorbed by the quartz. It was reported that the *d*-quartz preferentially adsorbed L-**29**, with an asymmetric adsorption of 6–20% at 0°C and 27–37% at 15°C, depending on the mesh size of the quartz used. Since in the two previous studies (58, 60) it was found that the presence of water had a deleterious effect on the asymmetric adsorption, the present report in which water was the solvent for **29** is quite remarkable and bears corroboration.

Attempts have been made (62) to use chiral crystals other than quartz as asymmetric adsorbents for racemic substrates. Chiral single crystals of $NaClO_3$, $NaBrO_3$, $NaIO_4{\cdot}3H_2O$, $Ni_2SO_4{\cdot}6H_2O$, sodium uranyl triacetate, and benzil were used in experiments involving attempted solid-state resolutions of such racemic and resolvable systems as chromium(III) and cobalt(III) tris(pentane-2,4-dionate), α-lipoic acid, penicillamine, and tartaric acid, using optical rotation at 546 nm as a criterion for asymmetric effects. No reproducible results were obtained, and the optical rotations observed were shown by careful replication experiments to be artifactitious. Some of these chiral crystals were also used in attempts to conduct stereoselective reactions on their surfaces, again with negative results.

With no supporting experimental evidence whatsoever, Klabunovskii (63) has recently proposed a three-stage pattern for the development of optical activity in nature. The small enantiomeric excesses first produced by photochemically mediated asymmetric syntheses or degradations (Sect. III-B-6) are enhanced by stereoselective adsorption on asymmetric mineral surfaces which, in turn, finally act as enantioselective agents to "catalyze the formation of organic compounds in high asymmetric yield." Whatever the merit of such speculations, the proposed second stage must be considered a random process from a prebiotic viewpoint, as must all of the successful asymmetric adsorption experiments involving quartz described above. This follows from the essentially random distribution of *d*- and *l*-quartz over the surface of the Earth. Frondel (64) has presented data on the relative frequency of *d*- versus *l*-

quartz from all over the world, in which the weighted average for 16,807 samples shows 50.5% *l*- and 49.5% *d*-quartz.

7. *Asymmetric Adsorption and Polymerization on Clays*

The common clay minerals kaolinite and montmorillonite have stacked planar structures comprised of alternating individual layers of repeating, covalently linked atoms. In the 1:1 clay kaolinite, the layers consist of two covalently linked sheets, one of tetrahedral silica and the other of octahedral aluminum hydroxide. In the 2:1 clay montmorillonite the octahedral aluminum hydroxide sheet is covalently linked above and below to two tetrahedral silica sheets. The individual layers in these clays are held together by hydrogen bonds or other weak forces. Both clays, but especially montmorillonite, can have other metals (e.g., iron or magnesium) isomorphically substituted in their crystal lattice, or as exchangeable cations on the outer surfaces of their layers (65). In neither clay is there any known chirality to the crystal structure (65, 66, 78) which could be implicated in diastereomeric interactions with chiral substrates, and there is thus no theoretical basis for expecting asymmetric effects involving clays. Nevertheless, a number of reports in the recent literature claim just such effects.

The first such report, by Degens et al. in 1970 (67), claimed that incubation at 90°C for 4 wk of 0.01 *M* aqueous solutions of D-, L-, and DL-aspartic acid in the presence of kaolinite resulted in $>25\%$ polymerization of the D-aspartic acid compared with $<3\%$ for the L-aspartic acid, with polymerization of the DL-aspartic acid falling halfway between. In a similar 3-day experiment the polymer yields were smaller, but again the L-aspartic acid was observed to polymerize to a greater extent. Jackson (68) later repeated these claims and made the additional observation that kaolinite adsorbed L-phenylalanine from pH 5.8 aqueous solution to a greater extent ($19.0 \pm 3.6\%$) than it did the D-enantiomer ($15.0 \pm 3.2\%$), and that at pH 2.0 adsorption of the D-phenylalanine remained the same ($15.3 \pm 7.1\%$), while that of the L-phenylalanine diminished ($9.8 \pm 4.3\%$). The results were interpreted as indicating that asymmetric adsorption and polymerization was occurring on the allegedly enantiomorphic *edge* faces of the kaolinite crystals, which acted as stereospecific templates for the preferential adsorption and polymerization of L-amino acids. It was further suggested that there may be a preponderance of such "L-fixing" minerals in nature.

In view of the potential implications for the prebiotic origin of molecular chirality, several groups immediately attempted a duplication of both the asymmetric adsorption and asymmetric polymerization experiments involving kaolinite. In 1973 Bonner and Flores (69) attempted to repeat the reported asymmetric adsorption of phenylalanine, using analytical criteria other than the UV absorption measurements previously employed (68). With both optical rotatory dispersion, gas chromatography, and thin-layer chromatography as diagnostic criteria for differential adsorption, no differences whatsoever were found in the adsorption of D- versus L-phenylalanine by kaolinite, at either pH 6 or pH 2.

Two papers followed shortly thereafter describing attempts to duplicate the reported asymmetric polymerization of aspartic acid by kaolinite. Following the earlier experimental protocol (67, 68) exactly, but using an internal standard (threonine) to improve the determination of aspartic acid concentrations on an amino acid analyzer, Flores and Bonner (70) found that kaolinite not only failed to promote a differential polymerization in D- versus L-aspartic acid, but also failed to induce any significant gross polymerization at all. McCullough and Lemmon (71) independently investigated the asymmetric polymerization claims described above using still other analytical criteria: (a) optical rotatory dispersion in the 300–190 nm region; (b) the use of ^{14}C-labeled aspartic acid followed by paper chromatography and X-ray film autoradiography; and (c) careful examination on an amino acid analyzer. They also found that kaolinite failed to show any detectable differential of even gross polymerization of aspartic acid enantiomers, although adsorption of the aspartic acid to the extent of 10–15% seemed to occur.

Another claim for an asymmetric effect of clays on amino acids is that of Thompson and Tsunashina (72), who studied the effects of exposure to kaolinite and montmorillonite on the enantiomers of phenylalanine and tyrosine in aqueous solution at pH 2–8 for 1–15 days. They found that the L isomers were "altered" faster than the D isomers, but their attention to the possible effects of bacterial contamination was unfortunately minimal. Jackson (73) later cites this paper "with certain reservations" as supporting his claims for asymmetric adsorption and polymerization, and suggests that the experimental conditions in the attempted duplication experiments (69–71) were not truly identical to his in that minute traces of crucially important "poisons" or "promoters" may have been present on the clay surfaces.

The controversy over stereoselective adsorption by clays was fanned further by Bondy and Harrington (74) in 1979, who attempted to assess the relative binding of "natural" versus "unnatural" enantiomers by clay. The ^{3}H-labeled natural substances L-leucine, L-aspartic acid, and D-glucose along with their labeled unnatural antipodes in $1.2–2.9 \times 10^{-8}$ M solution at pH 7.1 were each incubated at 30°C for 15 min with small amounts (2 mg) of montmorillonite (bentonite). The bentonite had been pretreated by heating at 90°C for 90 min with 0.5 N NaOH to eliminate bacterial contamination and remove any protein present. The incubated samples were then centrifuged and the resulting clay pellets were assayed for bound radioactivity. It was found that the natural enantiomers were adsorbed preferentially to the unnatural ones by an impressive extent, the adsorption ratios (i.e., bond counts) for natural/unnatural being leucine 6.5, aspartic acid 7.3, glucose 11.3. The authors then speculated that prebiotic clays might have assembled increasingly complex molecules from the primitive ocean, ultimately forming systems capable of replication, and that the binding differences noted above could account for the development of life forms based on L-amino acids and D-glucose. They also argued that the observed binding stereoselectivity implied that the clay itself must have had an (unspecified) asymmetric structure.

Needless to say, the Bondy–Harrington claims (74) immediately sparked a controversy regarding the chirality of clays (75), and quickly led to an attempt to duplicate their experiments. In 1981 Youatt and Brown (76) made a particularly careful study of the binding of ^{3}H-labeled L- and DL-leucine and L- and D-aspartic acid by bentonite from four different sources. They were especially careful to assure that the adsorbed decomposition products of the ^{3}H-labeled substrates did not produce artifacts, and they took additional precautions to sterilize the bentonite thoroughly and to dispense it aseptically. While 20 times higher substrate concentrations were used, the totals of bound substrates were less than those previously reported (74), and no preferential binding of the L-enantiomers whatsoever was apparent from the data. The authors pointed out that the observed binding was largely attributable to products of the radiochemical decomposition of the substrates.

An additional negative note on the asymmetric adsorption of amino acids by clays was provided by Friebele and co-workers (77) in 1981 who, paying particular attention to sterile techniques, incubated racemic samples of alanine, α-aminobutyric acid, valine, and norvaline with sodium montmorillonite at pH 3, 7, and 10 for 24 hr. The recovered adsorbed and nonadsorbed fractions (totaling 100%, with equal recovery of D- and L-enantiomers) were analyzed for their enantiomeric compositions by analytical gas chromatography (Sect. III-B-2-a). Their cumulative data led them to the conclusion that there was no significant stereoselective adsorption of the amino acid enantiomers by the sodium montmorillonite.

A discussion of clays would be incomplete without brief mention of the novel and controversial ideas recently advanced by A. G. Cairns-Smith of Glasgow regarding the role of clays in the origin of life (79). Ignoring the crucial role of chirality in self-replicating systems (5), Cairns-Smith postulated that the first replicating systems on Earth capable of evolution through natural selection were clay minerals with appropriate crystal defects, and that this inorganic "genetic material" was subsequently "taken over" by organic matter to form more efficient replicating structures as life evolved.

8. Conclusions

The biotic and abiotic chance mechanisms reviewed above have one characteristic in common: if an L isomer were to arise somewhere on Earth by a chance mechanism there would be an equal probability that the D enantiomer would arise somewhere else given comparable conditions, and if an L system were evolving toward life a D system would also be evolving elsewhere. Mann and Primakoff have recently pointed out (80) that "successful protein formation" at as few as 20 sites would have reduced the probability of dominance by a single chirality to $(1/2)^{20}$, or $\sim 10^{-6}$. Thus the argument in favor of statistical fluctuations in chance mechanisms has in it the implicit assumption that there were one or a very small number of terrestrial sites for the primordial molecular symmetry breaking. In other words, we must introduce "an arbitrary, non-statistical condition into what purports to be a strictly statistical phenomenon" to accommodate chance mechanisms. On the other hand, the probability that a particular prebiotic asymmetry was produced by a specific mechanism "would have increased linearly with the number of terrestrial sites" (80). Thus on the basis of the greater likelihood of a large number of possible symmetry breaking sites, random fluctuations are deemed much less probable as a source of asymmetry than are specific mechanisms (80).

Contradicting Wald's arguments (11) for the chance formation of life having a single chirality, Shapiro (81) has recently provided an amusing discussion of the utter improbability of producing life forms or replicating molecules by repetitive chance events on Earth, regardless of the several billion years of time available for the occurrence of such events. Thus the recent reiteration of Wald's arguments by Brode (82) and his accompanying dogmatic and arrogant advice that "attempts to explain the origin of natural optical activity through external, extrabiological agents . . . . should be abandoned" can safely be ignored, and we can turn our attention to the variety of determinate mechanisms investigated in recent years.

B. Determinate Mechanisms

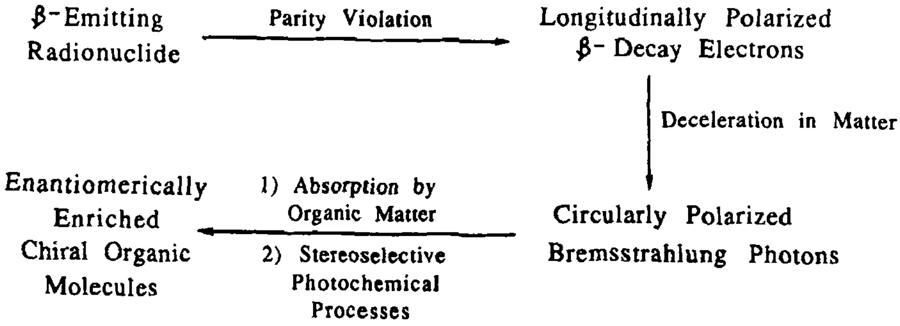
We have seen that determinate mechanisms for the origin of molecular chirality assume the existence of some intrinsic internal or environmentally external chiral physical force which acts in a stereoselective manner on racemic or prochiral primordial substrates to induce the production of a small net excess of one enantiomer. Such asymmetric effects are generalized extensions of the ordinary diastereomeric interactions familiar to chemists in many other contexts. Furthermore, it is generally assumed that most (but not all) of such chiral physical forces have operated in a unidirectional manner throughout the Earth's history, so that even though the asymmetric effect produced might be small, it was nevertheless persistent and possibly cumulative. Abiotic hypotheses involving determinate mechanisms have without question received the most experimental and theoretical attention during the past several decades.

1. Parity Violation

The principle of parity states that the laws of nature are invariant under spatial reflection. Thus any process that occurs in nature can also occur as seen reflected in a mirror, and the mirror image of an actual object is also a possible object in nature. In 1956 T. D. Lee and C. N. Yang, on considering certain anomalies in the decay patterns of θ and τ mesons, concluded that the parity principle might be invalid for certain weak interactions, such as those involved in β-decay. This Nobel prize-winning prediction was verified experimentally a year later by Wu and co-workers at Columbia, who found that the electrons emitted during the β-decay of ^{60}Co nuclei were in fact longitudinaly polarized in a predominantly "left-handed" fashion, that is, their spins were predominantly antiparallel to their direction of propogation. The principle of parity, which would have predicted an equal number of electrons of both parallel and antiparallel spins, was clearly violated (3, 83). It was not long before the potential biological implications of this fact were appreciated, and for this reason mechanisms for the origin of chirality involving various aspects of parity violation have received the most experimental and theoretical attention of all of the determinate mechanisms.

2. The Vester–Ulbricht Hypothesis

Shortly after the experimental demonstration of parity violation by Wu and co-workers, F. Vester and T. L. V. Ulbricht suggested a mechanism whereby such parity violation in nuclear events might be causally connected with the observed asymmetry of the molecules in the current biosphere. Charged particles (e.g., electrons) radiate when their motion is altered on deflection by another charged particle (e.g., a nucleus). Bremsstrahlung (German for "brake radiation") is the spectrally continuous radiation thus emitted when an electron decelerates on traversing matter. Longitudinally polarized electrons (having their spins parallel to their direction of motion) produce circularly polarized bremsstrahlung (270). The now famous Vester–Ulbricht (V–U) hypothesis (83) (Scheme 1) argued that as the longitudinally polarized electrons from nuclear β-decay were slowed down on traversing matter they produced circularly polarized bremsstrahlung photons which, on interacting


β⁻Emitting Radionuclide
Parity Violation
Longitudinally Polarized β⁻ Decay Electrons
Deceleration in Matter
Circularly Polarized Bremsstrahlung Photons
1) Absorption by Organic Matter
2) Stereoselective Photochemical Processes
Enantiomerically Enriched Chiral Organic Molecules

Scheme I

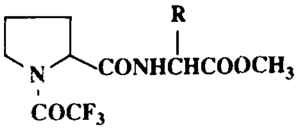
in turn with organic matter, produced optically active molecules by "absolute" asymmetric photochemical syntheses or degradations of the sorts known to occur with circularly polarized light (Sect. III-B-6). In 1962 Vester and Ulbricht then tested their hypothesis (84) by conducting 10 different organic reactions capable of producing optically active products in the presence of a variety of β-emitting nuclides, using various radioactivity levels, exposure times, and temperatures. The optical activity of the reaction products was measured by averaging multiple readings on a precision polarimeter. The average measurable rotation in 31 experiments was 0.0154±0.0161°, that is, zero within experimental error. The authors concluded that a definitive test of their hypothesis would require stronger radioactive sources and longer exposure times. In the following year Gol'danskii and Kharpov (85) attempted the β-decay electron irradiation (from ^{104}Rh) of some 14 different organic compounds comprised of 22 forms of solid racemates and optically active enantiomers. Polarimetric examination of the irradiated samples showed that no optical activity had been induced in any of the racemates, nor were differences noted in the effects of the radiation on any of the optical antipodes studied.

The field lay fallow until 1968, when Garay (86) in Hungary reported the first positive result. He dissolved D- and L-tyrosine separately in alkaline, aqueous ethanol, and irradiated each sample with ~0.36 mCi of $^{90}SrCl_2$ dissolved in each solution as the β-ray source. The UV absorption spectrum of each solution was then measured at several increasing time intervals. After 18 months the absorption band for the D-tyrosine was found to be considerably more diminished as compared to that of the L-tyrosine, an effect which was not observed in acidic solution or in an alkaline solution control using nonradioactive $^{88}SrCl_2$. Garay then suggested that the decomposition of the tyrosine in alkaline solution was actually an oxidative degradation reaction which was being biased toward the D enantiomer by the ^{90}Sr β-particles or their bremsstrahlung. Because of its potential importance as a mechanism for the abiotic origin of molecular chirality, Garay's positive report quickly encouraged a series of subsequent investigations by others into the possible validity of the V–U hypothesis. These investigations generally employed criteria other than UV absorption spectra for the recognition of enantiomeric excesses.

a. Criteria for Enantiomeric Composition. Historically, optical activity has been measured with a polarimeter, usually using monochromatic 589 nm (D-line) light from a sodium vapor lamp. More recently, with the advent of spectropolarimeters, optical rotations have been measurable over a continuous range of wavelengths, down into the ultraviolet. Such optical rotatory dispersion (ORD) measurements are advantageous, since optical rotation increases dramatically at shorter wavelengths approaching those characteristic of absorption bands of the chiral substrate, thus allowing more accurate measurements on compounds of low rotatory power. Since optical rotation is generally a linear function of enantiomeric composition, the latter can be estimated from optical rotation at a given wavelength, provided the rotation of one pure enantiomer is known at that wavelength. Thus in a mixture of D and L enantiomers, $\%\mathrm{D} = 50(1 + [\alpha]_m/|[\alpha]_p|)$, where $|[\alpha]_p|$ is the absolute value of the specific rotation of the pure enantiomer and $[\alpha]_m$ is the specific rotation of the mixture. For the polarimetric criterion to be valid, however, not only must the pure enantiomer be 100% resolved, but also enantiomeric mixture itself must be pure and uncontaminated.

These restrictions clearly jeopardize the application of polarimetry to the determination of enantiomeric compositions in crude mixtures of optically active substances, particularly when the components have low rotations or the mixtures are close to racemic. Accordingly, more reliable methods for estimating enantiomeric compositions have been sought. Perhaps the most widely used alternative criterion employed in recent years has been that of analytical gas chromatography (GC). The general procedure in this technique is to convert the enantiomer mixture to a volatile derivative which will allow quantitative resolution of the enantiomer derivatives by GC. Integration of the areas under the peaks corresponding to each enantiomer in the gas chromatogram then permits a quantitative analysis for each enantiomer in the mixture, that is, the determination of its enantiomeric composition. The interference by impurities in determining enantiomeric composition by this technique is eliminated, since they are either removed during preparation of the volatile derivative or are separated during the GC analysis itself. Another important additional advantage of GC is its applicability to minute quantities of material, quantities too small to be amenable to polarimetric measurement. Gas chromatography has been particularly useful in determining enantiomeric compositions of crude mixtures of amino acids resulting from studies of the V–U mechanism, as well as mixtures obtained from geological and marine sediments, meteorites, bone fossils, and soil samples, and the procedure has been suggested as part of a wet chemical probe for the detection of extraterrestrial life in future space exploration (see reference 87 for references to these studies).

Among the volatile derivatives employed in GC enantiomer analyses of amino acids have been diastereomeric derivatives, such as L-prolyl dipeptides (**32**) (88) and *N*-TFA-(+)-*s*-butyl esters (**33**) (87), which may be separated using conventional phases in the GC columns, or enantiomeric derivatives



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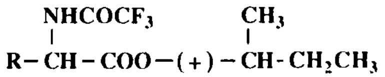
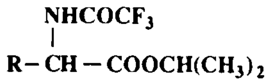


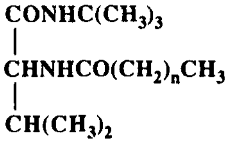
$$\overset{\displaystyle NHCOCF_3}{\overset{|}{R-CH}}-COO-(+)-\overset{\displaystyle CH_3}{\overset{|}{CH}}-CH_2CH_3$$

33



$$\overset{\displaystyle NHCOCF_3}{\overset{|}{R-CH}}-COOCH(CH_3)_2$$

34

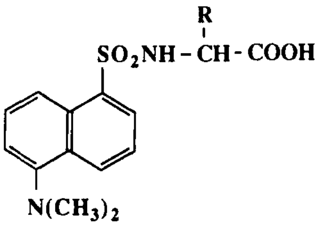


$$\begin{array}{l} CONHC(CH_3)_3 \\ | \\ CHNHCO(CH_2)_nCH_3 \\ | \\ CH(CH_3)_2 \end{array}$$

35

such as *N*-TFA-isopropyl esters (**34**) (87), which require optically active GC stationary phases such as *N*-lauroyl-(**35**, *n* = 10) or *N*-docosanoyl-L-valyl *tert*-butylamide (**35**, *n* = 20) (87, 89). The accuracy and reproducibility of GC analyses of D- and L-leucine mixtures converted to the derivatives **32**–**34** has been tested over a full range of enantiomeric compositions, with the findings that each method shows comparable accuracy (0.03–0.7% absolute error) and precision (0.03–0.6% standard deviation) (87). Analytical GC thus provides not only a sensitive and reproducible criterion for the estimation of enantiomeric composition, but it has proved applicable also to the determination of the *extents* of degradation of amino acid enantiomers during radiolysis or photolysis. To this end, an "enantiomeric marker" technique has been developed (90), using a known amount of one of the pure enantiomers as an internal standard during the GC analysis.

More recently, liquid chromatography (LC) has been used successfully for the resolution of enantiomers, either by the use of chiral supports in the LC columns (91, 274), or of chiral mobile phases in reversed phase LC. Examples of the latter include the resolution of racemic cobalt complexes (92), racemic amino acids as their dansyl derivatives (**36**) (93), as well as underivatized racemic amino acids using chiral Cu^{2+} L-proline complex as eluant (94). The latter procedure is particularly useful, since the order of elution of the amino



36

acid enantiomers may be reversed by using the enantiomeric Cu^{2+} D-proline complex as eluant, similar to the elution order reversal observed on using enantiomeric phases in GC analyses (89). The LC analyses, which have proved broadly applicable to amino acids and may be conducted using picomole quantities (94), share with GC analyses the advantage that possible interfering contaminants are automatically eliminated in the course of the analysis itself. Even greater sensitivity in the analysis of amino acid enantiomers has been achieved recently by Gassmann and co-workers (268), who were able to detect and quantitatively resolve dansyl DL-amino acid derivatives (**36**) at the femtomole level by means of high-voltage electrophoresis in capillary columns containing a Cu^{2+} L-histidine complex electrolyte, using laser fluorescence detection.

In the discussion of experiments involving the asymmetric adsorption of amino acids on quartz in Sect. III-A-6, we saw that radioactivity counting of DL-alanine having ^{3}H-labeled D- and ^{14}C-labeled L-enantiomers has also been used as a criterion for enantiomeric composition. This method, while accurate and occasionally useful, is unfortunately tedious and lacking in general applicability. Other physical methods for the determination of enantiomeric composition, including isotope dilution analysis (275) and various applications of nuclear magnetic resonance (NMR) (276), have been reviewed recently. These applications encompass the analyses of enantiomers other than those of amino acids. However, their general precision is considerably inferior to the GC and LC methods cited above.

b. Natural Radionuclides. In this section we summarize the results of experiments designed to test the V–U hypothesis or related processes using longitudinally polarized "left-handed" electrons (or their circularly polarized bremsstrahlung) obtained from the β-decay of the natural radionuclides ^{90}Sr, ^{90}Y, ^{3}H, ^{32}P, and ^{14}C. These experiments contrast others to be described later, which have employed polarized electrons or other chiral particles from "artificial" man-made sources to probe either the V–U mechanism itself or other processes that might shed light on it.

Because of certain misgivings about the experimental protocol employed by Garay in his earlier positive report of the asymmetric degradation of tyrosine by β-decay electrons from ^{90}Sr (86), Bonner in 1974 (95) undertook to reinvestigate the V–U mechanism using ^{90}Sr as a β-ray source under circumstances designed to obviate these difficulties. In particular (1) the relatively weak β-source previously employed (0.36 mCi of dissolved $^{90}SrCl_2$) was replaced by a bremsstrahlung source some 1.7×10^5 times as powerful, namely, 61.7 kCi of ^{90}Sr–^{90}Y oxide retained in dead storage in stainless-steel containers at the Oak Ridge National Laboratory; (2) the irradiations were conducted using primarily solid samples of D-, L-, and DL-amino acids, thus eliminating the effect of solvents, the radiolysis or photolysis of which would produce symmetrical radicals whose effects might obscure any actual asymmetric bias; and (3) ORD and analytical GC were used as criteria for an asymmetric effect, rather than the mere difference in the shapes of UV absorption spectra previously employed.

In these experiments, three identical groups of 21 separate amino acid preparations contained in small vials were placed in three metal containers which were lowered into the dose-calibrated 61.7 kCi bremsstrahlung source mentioned above, to be recovered and analyzed at increasing time intervals in the future. The first group of samples was retrieved after 124 days (dose $= 1.1 \times 10^8$ rads), and found to be minimally decomposed. The second samples were retrieved after 1.34 yr (dose $= 4.1 \times 10^8$ rads). Careful GC analyses of several of the irradiated samples, interspersed "back to back" with analyses of nonirradiated controls, showed that the former, both in the solid state and as Na and HCl salts in solution, were optically inactive within experimental error (95). It was concluded that longer irradiation times might be needed to see an asymmetric effect, since the maximum extent of degradation noted for solid leucine was only 16.2%, as measured by the GC "enantiomeric marker" technique (90). The final set of samples was only recently retrieved and analyzed, after 10.9 yr of irradiation and a dose of $\sim 2.5 \times 10^9$ rads (96). Crystalline DL-leucine, DL-norleucine, and DL-norvaline were found to have undergone 47.2, 33.6, and 27.4% radiolysis, respectively, but there was no GC evidence whatsoever for any asymmetric degradation, that is, the enantiomeric compositions of all irradiated samples were still racemic within experimental error. Both D- and L-leucine underwent 48% radiolysis, in agreement with that of the DL sample, and showed 2.4–2.9% radioracemization (Sect. III-B-2-c).

Bonner and Liang (90) have recently suggested that the primary reason for the failure of the V–U mechanism to provide an asymmetric effect in the ^{90}Sr bremsstrahlung radiolysis experiments involved certain intrinsic properties of the bremsstrahlung themselves. In Figure 5 we see that bremsstrahlung has a continuous energy spectrum ranging from zero to the maximum energy of the β-decay electron, with the vast majority of the bremsstrahlung intensity lying

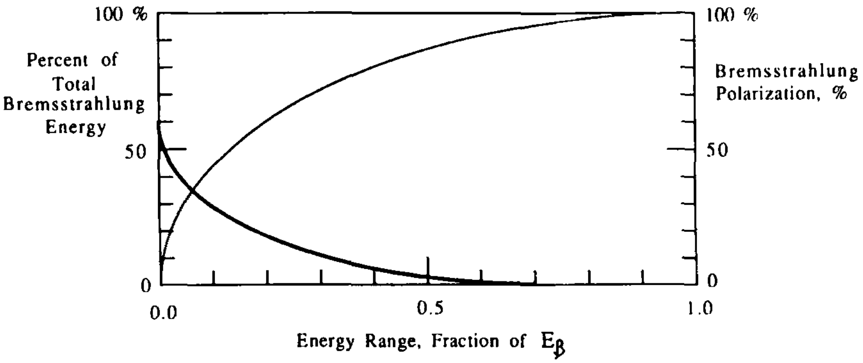


Figure 5. Bremsstrahlung intensity and circular polarization as a function of energy. (E_β = maximum energy of β-decay electron).

in the low-energy end of the spectrum (97). On the other hand, the circular polarization of the bremsstrahlung photons ranges from zero at the low-energy end to ~100% at the high-energy end of the spectrum (98). Thus the preponderant low-energy bremsstrahlung, with energies in regions most capable of inducing photochemical processes on absorption by matter, is of insufficient circular polarization to engender an asymmetric effect, while conversely the high-energy, well-polarized bremsstrahlung are of insufficient intensity and in the wrong energy domain to induce such an effect.

The possible asymmetric interaction of longitudinally polarized β-radiation with amino acids was investigated in another way by Akaboshi and co-workers in 1979 (99). They irradiated D-, L-, and DL-alanine in quartz tubes at 77 K with β-rays from ^{90}Y, produced in turn by separate irradiation of ^{89}Y with thermal neutrons. The extent of free radical formation (R–β) in each sample was measured by ESR techniques, and the results were standardized by comparing them with free radical production (R–γ) observed in the same samples on irradiation with unpolarized ^{60}Co γ-rays. The (R–β)/(R–γ) ratio for D-alanine was 14–21%·higher than that for L-alanine. When the experiments were repeated with nonpolarized β-rays from a Van de Graaf generator, no differences in the (R–β)/(R–γ) ratio were found for the alanine enantiomers (100), nor were differences noted when irradiations were conducted in frozen solutions (101). The observed asymmetric effect was inversely proportional to the β-ray dose, the lower the dose the larger the effect. These puzzling results were interpreted as possibly due to different interactions of the crystal structures of the two enantiomers with the polarized β-rays (101). The observations of stereoselective radical formation in alanines were subsequently confirmed by Conte and co-workers (102) who, using the β-

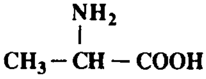
radiation from a ^{90}Sr–^{90}Y source and employing similar ESR techniques for measuring free radical production, found the magnitude of the effect "quantifiable as about 13%."

In an attempt to establish whether β-rays or their bremsstrahlung were responsible for the stereoselective radical formation in D- and L-alanine, Akaboshi and co-workers subsequently extended their experiments to include β-radiation from ^{3}H (103). In these experiments each of the alanine enantiomers was mixed with a small amount of highly radioactive (82.7 Ci/mM) L-(3-^{3}H)alanine, so that the β-rays would be emitted "internally" within the alanine samples. In this way the contribution of the bremsstrahlung to any asymmetric effect should be much less than in the ^{90}Y irradiations, since the low energy β-rays from ^{3}H produce far less bremsstrahlung. The samples were stored at 77 K for 1 yr (total dose $= 3.4 \times 10^4$ rads), whereupon the usual ESR measurements were made along with the customary ^{60}Co γ-ray controls. Again, the $(R-\beta)/(R-\gamma)$ ratios were some 13% higher for D- than for L-alanine as solids. When dissolved on D_2O and kept at 77 K for a year, the alanines showed similar stereoselectivity for radical formation, $(R-\beta)/(R-\gamma)$ again being greater for the D enantiomer by $\sim 16\%$. The effect again dropped off with increasing dose, suggesting a saturation effect. The authors concluded that the polarized β-rays, rather than their bremsstrahlung, were responsible for the stereoselective interactions observed between the two enantiomers, but attempted no theoretical explanation for the effect. They later studied the relative efficiencies of ^{3}H β-rays and ^{60}Co γ-rays in producing radicals in alanine, finding that the β-rays were more effective by a factor of 1.25 at 25°C and 1.58 at -196°C (104).

In an experiment designed to test the V–U hypothesis with yet another natural β-emitter, Darge and co-workers (105) in 1976 undertook the asymmetric radiolysis of D,L-tryptophan using ^{32}P β-rays. The racemic amino acid in frozen aqueous solution (-25°C) was exposed to the β-radiation from 5 mCi of codissolved ^{32}P-phosphate for 12 wk, whereupon the crude reaction mixture was diluted and examined. A gross radiolysis of 33% (estimated by UV absorption spectra) was reported, as was an astonishing 19% enrichment of the D-tryptophan in the undestroyed residue. The 19% enrichment was estimated by comparison of the optical rotation of the crude, dilute radiolysis sample with that of pure L-tryptophan at 220 nm, and was based on observed optical rotations of $-0.0036°$ for L-tryptophan and $+0.0007 \pm 0.0004°$ for the irradiated sample.

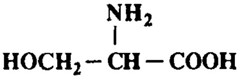
Because the remarkably large effect claimed above was based on such small observed optical rotations, and because the data had already been used uncritically by others in theoretical calculations, Bonner and co-workers (106) undertook a careful duplication of the Darge experiment using, however, analytical GC for the estimation of the extents of both radiolysis and enantiomeric enrichment. In duplicate experiments, again using nonradioactive controls for comparison, gross degradations averaging 43.5% were observed, but no evidence whatsoever for stereoselective radiolysis was found. Thus the average GC analyses of the irradiated samples were D-tryptophan, 50.5% (control, 50.9%) and L-tryptophan, 49.5% (control, 49.1%). In later extensions of these studies Blair and Bonner (107) employed longer irradiation times with tryptophan and lower temperatures (−196°C) in ^{32}P β-irradiations with DL-leucine. In the latter experiments, again using GC criteria, 20–30% gross radiolysis was observed but, as with tryptophan, no concomitant asymmetric bias whatsoever was found within experimental error.

A novel use of ^{32}P in an unusual stereoselective reaction was reported by Akaboshi and co-workers (108) in 1978. ^{32}P-Phosphate was mixed with ^{14}C-labeled D- or L-alanine (**37**) and with D- or L-serine (**38**). As ^{32}P undergoes β decay, it produces "hot" recoiled ^{32}S atoms. These were allowed to impinge on the labeled enantiomers of **37** and **38** to produce D- or L-cysteine (**39**), which was subsequently oxidized to D- or L-cysteic acid (**40**) for analysis by



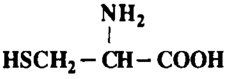
$$\mathrm{CH_3-\overset{\overset{NH_2}{|}}{C}H-COOH}$$

37



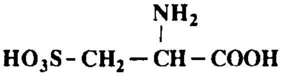
$$\mathrm{HOCH_2-\overset{\overset{NH_2}{|}}{C}H-COOH}$$

38



$$\mathrm{HSCH_2-\overset{\overset{NH_2}{|}}{C}H-COOH}$$

39



$$\mathrm{HO_3S-CH_2-\overset{\overset{NH_2}{|}}{C}H-COOH}$$

40

paper chromatography and radioautography. It was observed that the D-enantiomers of **37** and **38** were converted to **39** more readily (2.8 times for **37**, 4.8 times for **38**) than the corresponding L-enantiomers. Control experiments in which the ^{32}P was shielded from the substrates led to negligible conversions of **37** and **38** into **39**, and it was concluded that the conversions were brought about by the recoiled ^{32}S atoms. The authors were noncommital about the D > L stereoselectivity observed in the conversion, since they did not know the mechanism of the reaction. The report has not yet been independently corroborated.

In 1972 Bernstein et al. (109) voiced a criticism, later also emphasized by Bonner (95), of the 1968 experiment of Garay (86), namely, that his ^{90}Sr β-

radiolyses of tryptophan were conducted in aqueous solution, where H atoms, OH radicals, and hydrated electrons produced by radiolysis of the solvent would dominate subsequent chemical reactions of the solute, thus obscuring any possible asymmetric effect. They suggested that such experiments would better be done using amino acids in the solid state. Accordingly, they decided to examine a number of crystalline ^{14}C-labeled amino acid samples of high specific radioactivity (300–600 mCi/mol) which had been synthesized for other reasons at the Lawrence Berkeley Laboratory, University of California some 12–24 yr earlier. These samples had been undergoing self-β-radiolysis in the solid state with the ^{14}C β-rays during the intervening years, and it was proposed that their examination for asymmetric radiolysis might provide a more valid test of the V–U hypothesis than did Garay's experiment. Accordingly, five of the racemic amino acid samples were examined on an amino acid analyzer for percent decomposition and in the ORD mode of a spectropolarimeter for optical activity. No optical rotations were observed within the sensitivity (0.002°) of the spectropolarimeter. The failure to detect differential radiolysis was attributed either to (1) the fact that the enantiomers might have reacted equally to the polarized β-radiation, or (2) the possibility that since ^{14}C β-rays have a low kinetic energy (156 keV maximum) and the degree of polarization is known to be proportional to the kinetic energy (83), the ^{14}C β-particles may not have had sufficient polarization to cause an observable asymmetric effect.

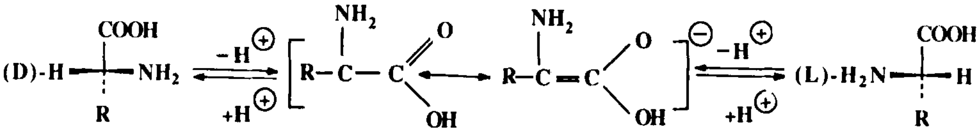
To verify these studies, a larger array of the previous ^{14}C-labeled amino acid samples was subsequently reexamined by Bonner et al. (110), using analytical GC as the criterion for both gross and differential radiolysis. In racemic samples 17–25 yr old which had received $5.4–11.4 \times 10^7$ rads of ^{14}C self-β-radiation, gross radiolysis ranged from 17 to 68%, but once again the enantiomeric compositions of all samples proved racemic within experimental error. In the same study, several optically active ^{14}C-labeled samples of comparable age were examined at the same time, with the finding that radioracemization (Sect. III-B-2-c) did not necessarily accompany the radiolysis of amino acids in the solid state.

While ^{14}C has a half-life of only ~5700 yr, it is continuously replenished in the upper atmosphere by the ^{14}N(n,p)^{14}C reaction resulting from the action of neutron secondaries produced by cosmic radiation (111). By atmospheric mixing this ^{14}C would become rapidly incorporated into the molecular environment of the primitive Earth, and would have been available at a low level since the prebiotic era (112). In the ^{14}C radiolyses cited above it was calculated (110) that between 6000 and 36,000 molecules were decomposed for every primary β-particle emitted, and it was suggested that the obvious plethora of degradations brought about by subsequent secondary processes could reduce any actual asymmetric effect to experimentally undetectable levels. While such low levels of ^{14}C-produced asymmetry might be experimentally undetectable in the laboratory, they have nevertheless been persistent since prebiotic times, and it has been suggested that the β-radiation from ^{14}C *within* the prebiotic organic molecules themselves might have provided a small but persistent chiral bias (112) which could later be amplified to the current state of biomolecular homochirality.

Of the many experiments conducted by irradiating amino acids with the β-radiation and/or bremsstrahlung from natural radionuclides, only those of Akaboshi and co-workers describing stereoselective formation of free radicals in alanine enantiomers during irradiations involving ^{90}Y (99–101) or ^{3}H (103) have led to experimentally reproducible (102) positive results. While these experiments may have implications for and a vague connection with the V–U hypothesis, they certainly do not constitute a direct test or confirmation of it (nor has this been claimed). All those experiments with the natural radionuclides ^{90}Sr–^{90}Y, ^{32}P, or ^{14}C which attempted to test the V–U hypothesis directly, however, have led to negative or nonreproducible results. A particular weakness in the V–U hypothesis seems to center on the circularly polarized bremsstrahlung step in the mechanism (Scheme 1). In 1975 Keszthelyi and Vincze (113) attempted to establish the validity of this step experimentally by measuring the absorption of ~100% right- or left-circularly polarized 14.4-keV γ-ray photons (equivalent to low-energy bremsstrahlung) from ^{57}Fe by the D- and L-enantiomers of tryptophan and tyrosine. No differences within experimental error ($\sim 10^{-3}$) were observed in the absorption by the enantiomers of either substrate, and the authors concluded than any asymmetric absorption of circularly polarized 14.4 keV photons was very small, if indeed it existed at all. The difficulties regarding the circular polarization, intensity, and energy distribution of bremsstrahlung as they impact on the V–U mechanism have already been cited (Figure 5), and Keszthelyi and Vincze (113) have pointed out further that the photochemically more important low-energy bremsstrahlung (<30 keV) would have been absorbed and could not have reached the samples in the ^{90}Sr–^{90}Y bremsstrahlung experiments previously conducted (95, 96).

Walker (114) has cast additional doubt on the circularly polarized bremsstrahlung step in the V–U mechanism, arguing that it should not be operative in *short-term* β-irradiations, as in the laboratory. His calculations showed that far too small a fraction of the total energy of the electrons could appear as photons capable of causing observable photochemical effeccts. In *long-term* irradiations in nature, however, the V–U mechanism might still be viable, since "even a minute preference for one enantiomer may be amplified by (subsequent) replicative or autocatalytic steps into complete dominance during biological evolution" (114).

c. **Radioracemization.** Racemization, which can be thought of as the reverse of optical resolution, is a process involving the conversion of one enantiomer of an optically active compound into a 1:1 mixture of both enantiomers. Given a mechanism that allows it to occur, racemization is thermodynamically a spontaneous process, since its free energy is negative and it is attended by an increase in entropy (115). For amino acids in neutral or alkaline solution the accepted mechanism for racemization involves reversible removal of the α-H atom as a proton, leaving a configurationally labile, resonance-stabilized carbanion (**41**) which may reprotonate "on either side" to give the racemate (Scheme 2). In acid solution, in the solid state, or in a mineral matrix the mechanism may be more complex, but the overall result is the same (116). If the specific rate for racemization of a natural L-amino acid is known under given conditions, a measurement of the L/D ratio for this amino acid partially racemized under the same conditions allows an estimate of the age of the amino acid in question, and hence of the milieu in which it was found. This enantiomer ratio dating technique for amino acids has been widely employed to estimate the ages of geological sediments, shells, bones, teeth, corals, and fossils, and the average temperatures that fossils have experienced since their deposition. The numerous applications of the amino acid dating technique, as well as its details, assumptions, and countless pitfalls were meticulously summarized in 1977 by Williams and Smith (116).

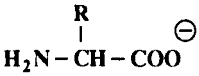


41

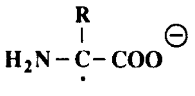
Scheme 2

In their examination of aging samples of several optically active ^{14}C-labeled amino acids, Bonner and co-workers (110) noted that small amounts of racemization seemed to accompany the β-radiolysis of several of the samples. Since racemization had been noted previously during γ-irradiation of aqueous solutions of mandelic acid (117) as well as on storing samples of ^{3}H-labeled amino acids (118), and since such *radioracemization* (i.e., racemization induced by ionizing radiation), had not been considered in any of the asymmetric radiolysis studies involving the V–U hypothesis, Bonner and Lemmon undertook to investigate the phenomenon or radioracemization in greater detail.

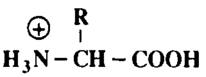
In their first studies in 1978, crystalline D- and L-leucine as well as aqueous solutions of their sodium and hydrochloride salts were exposed to increasing doses of γ-radiation from a 3000-Ci ^{60}Co γ-ray source, and the extents of radiolysis and radioracemization were estimated using analytical GC (119). γ-Ray doses that caused 68% radiolysis of solid leucines left residues that were ~5% racemized. Radiolysis and radioracemization of the dissolved sodium salts were even greater, and were proportional to γ-ray dosage over the range employed ($1–27 \times 10^6$ rads). At the highest dose the sodium salt samples had suffered 73.6% radiolysis and 9.2% racemization. Interestingly, the dissolved hydrochloride salt samples showed comparable degradations with increasing γ-ray dose, but only negligible radioracemization. These studies were later expanded (120) to include six other crystalline amino acids and their sodium and hydrochloride salts in aqueous solution. Radiolyses of the solid samples to the extent of 38–68% were accompanied by 1.6–5.6% radioracemization. Again the dissolved sodium salts were more susceptible to both radiolysis and radioracemization, while the dissolved hydrochloride salts were quite immune to radioracemization, even when radiolyses occurred to the extents of 52–64%. The differences in the radioracemization susceptibilities of the amino acids in alkaline or acidic media were rationalized in terms of the differing stabilities and ease of formation of the α-radicals **43** (produced in alkaline solution from the substrate anion **42**) and **45** (produced in acidic solution from the substrate cation **44**), resulting from the attack of HO•radicals formed by solvent radiolysis. The radical anion **43** can be stabilized as a highly symmetrical resonance hybrid, which is not the case for the radical cation **45**.


$H_2N-\overset{\overset{R}{|}}{CH}-COO^{\ominus}$

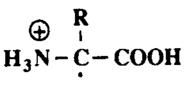
42


$H_2N-\underset{\bullet}{\overset{\overset{R}{|}}{C}}-COO^{\ominus}$

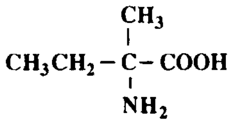
43


$\overset{\oplus}{H_3N}-\overset{\overset{R}{|}}{CH}-COOH$

44


$\overset{\oplus}{H_3N}-\underset{\bullet}{\overset{\overset{R}{|}}{C}}-COOH$

45


$CH_3CH_2-\underset{\underset{NH_2}{|}}{\overset{\overset{CH_3}{|}}{C}}-COOH$

46

The nonprotein amino acid isovaline (**46**), which has been isolated from a type II carbonaceous chondrite which fell to Earth near Murchison, Victoria, Australia in late 1969, possesses no α-H atom, and thus cannot racemize by the ordinary α-H abstraction mechanism (Scheme 2) open to ordinary amino acids (121). Thus it has been argued (122) that the enantiomeric composition of **46** in the Murchison chondrite, which has been found by GC analysis to be close to racemic (121), must be that which prevailed at the time of its original synthesis in the meteorite parent body, and that therefore other racemic amino acids isolated from meteoritic sources in general must have always been racemic and hence of nonbiogenic origin. It was therefore of some cosmological interest when Bonner et al. (123) found that isovaline in the solid state was approximately as subject to radioracemization as were the protein amino acids, although its sodium salt in aqueous solution was completely immune. The absence of radioracemization for the sodium salt of **46** in solution is in accord with the impossibility of intervention of the Scheme 2 mechanism for its racemization, owing to its lack of an α-H atom. Since meteorites have received a radiation dose of over 5×10^8 rads from cosmic rays and their own radioactive constituents during their 4.5×10^9 yr existence (124), it is clear that significant radioracemization of their amino acids could have occurred during this period. Thus the approximately racemic composition (121) of the **46** isolated from the Murchison meteorite could be the result of its radioracemization, making questions about the racemic composition of other meteoritic amino acids and their biogenic or abiogenic origin indeterminate (123). It has also been emphasized that the possible intervention of radioracemization jeopardizes the indiscriminate applicability of the amino acid enantiomer ratio technique for the dating of geochemical or paleontological specimens (125).

To make their radioracemization studies more realistic from geochemical and prebiotic viewpoints, Bonner et al. subsequently examined the effects of several mineral surfaces on the radioracemization of amino acids under varying conditions. The surface of powdered quartz appeared not to influence the radiolysis or radioracemization of L-leucine appreciably, but when a commercial amorphous silica preparation (Syloid 63) having a vastly greater surface area was used, both radioloysis and radioracemization of L-leucine were greatly enhanced (126). These experiments were then extended to include the clay minerals kaolinite and bentonite. Each clay enhanced the ease of both radiolysis and radioracemization of leucine, with bentonite showing a slightly larger effect (127). The several mineral surfaces studied thus appeared to make amino acids more susceptible to radiolysis and radioracemization, rather than to protect them from these effects.

Early in these studies it was emphasized that the phenomenon of radioracemization could only have a deleterious effect on the efficacy of the V–U mechanism (119, 120). Depending on the rate of appearance of an enantiomeric excess by stereoselective radiolysis, as compared with the rate of its radioracemization, it would be possible that no enantiomeric excess whatsoever might accrue before gross radiolysis was complete. The relative values of the rate constants for these two competing processes would determine which one prevailed in their natural setting, and whether the V–U mechanism could produce a net stereoselective degradation or synthesis in that setting (120). Radioracemization, particularly in connection with the enhancing effect of mineral surfaces, also potentially invalidates the calculations and conclusions of Keszthelyi and co-workers (128) that molecular asymmetry caused by β-decay could survive racemizing influences during long geological epochs, although it was recently concluded on experimental grounds that radioracemization itself probably would not have a *totally* negating effect on the V–U mechanism (127).

d. β-Decay and Crystallization. We have seen (Sect. III-A-2 and 3) that the generation of optical activity by spontaneous resolutions during the crystallization of conglomerates, while potentially very efficient, is a random process, affording one enantiomer one time and its antipode the next. It is not surprising, therefore, that attempts were made early on to see if the parity violation inherent in β-decay might be utilized to bias the random process of spontaneous resolution of conglomerates toward the selective crystallization of one enantiomer. While these attempts have no direct bearing as such on the V–U mechanism of Scheme 1, they nevertheless represent additional early attempts to link parity violation on the elementary particle level mechanistically with the broken symmetry on the macro level observed in the current biosphere.

In 1975 Kovacs and Garay (129) carried out crystallizations of sodium ammonium DL-tartrate, [Na^+, $NH_4^+({}^-OOC-C^*H(OH)-C^*H(OH)-COO^-)$; DL-**47**] from 45% aqueous solution at 1–4°C in the presence of the chiral β-particles and their bremsstrahlung, resulting from the β-decay of 0.16 mCi of codissolved $K_3{}^{32}PO_4$ per sample. Parallel crystallizations using nonradioactive $K_3{}^{31}PO_4$ were conducted as controls. In 63 independent crystallizations a slight preference was found for the crystallization of L-**47**, as indicated by the CD signal at 225 nm, whereas with 63 controls an approximately equal distribution of D-**47** and L-**47** was obtained. The magnitude of the bias, as expressed in medians of the CD signals, was 0.0 for the controls and 0.2 for the irradiated samples, the shift being "significant at the 0.1% level." The authors suggest that the effect might have been due to the enhancement of the number of crystallization centers of the L-**47** by the β-particles.

Kovacs (130) later expanded these experiments, performing a total of over 900 additional ^{32}P-irradiated and control crystallizations and using several higher levels of radioactivity. Again the "unnatural" L-(+)-**47** crystallized preferentially, with the bias increasing at higher radioactivity levels. Thus at radioactivities of 0.1, 1.6, and 5.0 mCi/sample, optical rotations at 215 nm of +2.41, +11.90, and +16.07 (deg·cm^2/decimole) were observed corresponding, respectively, to optical purities for the L-(+)-**47** of 0.035, 0.174, and

0.235%. All control crystals were optically inactive. Separate experiments were conducted to show that optically active contaminants were not responsible for the stereoselective bias observed. Higher yields of crystalline material and smaller crystals were obtained in the irradiated crystallizations than in the controls, suggesting that more individual crystals were formed (i.e., there were more nucleation sites) in the presence of β-particles than in their absence. Since some 10^5–10^6 crystals were deposited by the end of each experiment, since 10^8–10^9 β-particles/min were injected into each irradiated sample during each experiment, and since nucleation takes several days, clearly an overwhelming excess of β-particles over crystal nuclei existed during the course of each irradiated crystallization. Kovacs accordingly suggested again that the stereoselectivity in crystal seed formation was due to the presence of the β-particles, and attempted to analyze their effect as opposed to the subsequent effects of secondary processes. Finally, he proposed a scheme whereby the autocatalytic nature of crystallization might have induced net molecular chirality on the primitive Earth by the triggering mechanism of stereoselective crystallization induced by β-decaying isotopes (130).

It is difficult to find fault with Kovacs' numerous and carefully conducted crystallization experiments. One only wishes, however, that his control experiments had been conducted using nonchiral ionizing radiation such as γ-rays, rather than no radiation at all. Similarly, since "hot" recoiled ^{32}S atoms produced on β-decay of ^{32}P have been reported to produce stereoselective effects (108), the possibility exists that these might be implicated in Kovacs' stereoselective crystallizations in the presence of ^{32}P. This could perhaps be checked by using β-emitters other than ^{32}P to bias the crystallizations. Until such experiments are performed, one cannot accept the validity of Kovacs' conclusions completely uncritically.

3. *Direct Effects of Chiral Radiation*

Since the experiments discussed above directly testing the V–U mechanism by using antiparallel (AP) spin, "left-handed" electrons (and their accompanying bremsstrahlung) from various natural β-emitting radionuclides have been uniformly negative or nonreproducible, a number of investigators have turned to the use of longitudinally polarized electrons and other chiral elementary particles produced by man-made particle accelerators and polarizers of one sort or another. Such "artificially" produced particles offered a number of advantages over the β-radiation from natural radioisotopes: (1) the particle energies could frequently be selected to encompass a desired range; (2) the irradiations could be done directly on the crystalline target substrates, minimizing the production and effect of bremsstrahlung and thus partially bypassing that step of the V–U mechanism; (3) the longitudinal polarization of the "artificially produced" particles was frequently accurately known and generally higher than that of the "natural" β-particles, often approaching 100%; and (4) most importantly, the AP spin of "left-handed" particles could generally be reversed at will to a parallel (P) spin, "right-handed" polarization, thus providing the possibility of a "symmetry check" or test of the theoretical requirement for reversal of any observed stereoselective bias on reversal of the longitudinal polarization of the particle. In the next three sections we examine the design, results, and interpretations of the numerous experiments with "artificially" produced chiral particles that have been conducted during the past dozen years.

a. Electrons. An electron represents the simplest quantum mechanical system, having just two quantum states, spin parallel (P) or spin antiparallel (AP) to its direction of motion. In an ordinary beam of electrons there is an equal number of electrons in each state, and the beam is said to be unpolarized. A longitudinally polarized beam of electrons is an assembly having a net excess of one spin polarization along its reference direction. The magnitude of the polarization is given by: % polarization $= 100[n(\mathrm{P}) - n(\mathrm{AP})]/[n(\mathrm{P}) + n(\mathrm{AP})]$. The several experimental methods for producing longitudinally polarized electron beams have recently been reviewed (131).

To eliminate the difficulty of low-energy and poor circular polarization of the β-decay bremsstrahlung (Figure 5) inherent in their nonstereoselective ^{90}Sr–^{90}Y bremsstrahlung irradiations of amino acids, Bonner and coworkers in 1975 (132) turned their attention to the use of longitudinally polarized electrons from a linear accelerator source. A beam of 50–180 V electrons from a rotatable cathode was scattered by impinging on a stream of mercury atoms in an evacuated oven. Selected groups of the transversely polarized scattered electrons were then accelerated to 120 keV, and finally converted to longitudinally polarized electrons by magnetically bending the beam through a relativistic 90° angle in its direction of travel. By selecting the proper angle of the rotatable cathode, either P or AP 120 KeV longitudinally polarized electrons could be produced.

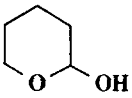
The beam of polarized electrons was allowed to impinge directly on solid samples of DL-leucine held in place in the evacuated target area by a Collodion binder. Irradiations were conducted with P or AP spin-polarized beams having 13–23% net polarization for time periods permitting ~53–75% gross degradation of the sample, whereupon the undecomposed leucine was recovered from the crude irradiated mixture and analyzed by GC for enantiomeric composition and percent degradation. Three "natural" AP spin irradiations selectively decomposed the D-leucine in the racemic target, leaving the "natural" L-leucine in excess, with enantiomeric excesses (e.e. = %D − %L) of −1.42 −0.86, and −0.60% for 52.9, 50.9, and 54.9% gross degradation, respectively. Three P spin irradiations did just the reverse, selectively decomposing the L-leucine component with e.e.'s of +0.80, +0.74, and +1.14% for 73.9, 75.6, and 76.3% gross degradation, thus providing a consistent "symmetry check" for the stereoselective bias. However, six other irradiations with 120 keV P or AP spin electrons gave no asymmetric effect, nor did two irradiations with 60 keV AP spin electrons.

Shortly after this positive report, Keszthelyi (133) pointed out that neither the gross nor the stereoselective degradation of leucine by polarized electrons claimed above could have been caused by accompanying bremsstrahlung produced in the target. He calculated that even if the entire bremsstrahlung energy had been absorbed by the sample, less than 0.1% of the total degradation could have been produced by the bremsstrahlung. Walker (114) had independently arrived at a similar conclusion. In their reply to Keszthelyi, Bonner and co-workers (133) hypothesized that if bremsstrahlung photons were excluded as a cause of the reported asymmetric effect, additional sources of chiral photons might have been available to produce stereoselective photolysis, namely, circularly polarized phosphorescence or fluorescence radiation emitted by the chiral substrate after excitation by the chiral primary electrons. At this stage the mechanism of the reported stereoselective radiolysis remained an open question.

The potential importance of this claim for the stereoselective degradation of leucine by longitudinally polarized electrons soon prompted an attempt to duplicate the observations. In 1979 Hodge and co-workers (134) conducted the degradation of DL-leucine with 36–47% polarized P and AP spin electrons of 120-keV energy produced by an alternative polarized electron source, one based on the Fano effect (131). The irradiated samples were analyzed by GC by the same procedures employed by Bonner and co-workers (132). A total of 27 irradiations was conducted, with the last five runs (after correspondence with Bonner and co-workers) approximating as closely as possible the experimental conditions previously employed (132). In 14 of the experiments using P spin electrons the percentage of D-leucine in the irradiated sample was 50.07 ± 0.03, while in 13 AP spin-electron irradiations the percentage of D-leucine was 50.05 ± 0.03. Thus no stereoselective radiolysis was found, the earlier positive report was not corroborated, and the reasons for the discrepancy remain obscure, although Bonner and co-workers later suggested the possibility that unknown amounts of radioracemization might tip the balance between no effect and a marginally observable one (135).

A related search for a stereoselective effect with beams of chiral particles has been made recently by Walker (136). He pointed out that the previous β-radiolyses with electron beams were not particularly sensitive, since 80–90%

of the radiolysis was induced by secondary electrons (δ-rays) which do not carry the polarization of the primary β-particle. This resulted in a 5- to 10-fold "dilution factor" for any asymmetric effect produced by the primary polarized electron. He averted this problem by using a 50:50 mixture of crystals of the pure D and L enantiomers of 2-hydroxytetrahydropyran (**48**),


48

rather than a racemic mixture at the molecular level. Each crystal was ground to a size that would exceed the ranges of the secondary δ-rays, so that each time a primary particle interacted with one enantiomer of **48** its entire effect would be deposited in that same enantiomer. Radiolysis was conducted to the extent of 7–8%, and the irradiated substrate was examined by CD. No enantiomeric excess could be detected within the accuracy of the measurement (~2% e.e. in the radiolyzed portion of the sample).

Two somewhat related studies with accelerator-produced electrons are worth noting. In 1975 Ulrich and Walker (137) produced solvated electrons that were "inherently chiral" because of the chirality of the molecules of their solvent cages, then allowed them to react with an enantiomer of an added chiral solute. The assumption was that an electron confined to a solvent of one chirality might show a different probability of reaction with D- and L-enantiomers of a chiral solute. They produced solvated electrons in L-2-methyl-1-butanol and D- or DL-2-butanol by pulse radiolysis, then studied their interactions with L-3-chlorobutyric acid and (−)-camphor, following the first order decay constants for the solvated electrons in the D- or L-solvent with the L-solutes. No preferred reaction rates were found, indicating an absence of stereoselectivity within the sensitivity of their measurements.

Close has reported (138) on experiments involving the interactions of P and AP spin electrons with protons. The AP spin electrons appeared to have a slightly greater tendency to interact with protons than did the P spin electrons, the AP excess being 1 event in ~10^5. Thus there are "both left-handed and right-handed electrons, but it is the former that prefer to interact in the real world."

Finally, theoretical calculations have recently been made (153) of the net helicity induced in an unpolarized electron beam after being scattered by molecules of an optically active medium, a phenomenon analogous to the circular polarization of photons by Rayleigh scattering from chiral molecules. For chiral carbon compounds the net helicity was calculated to be ~ 1 part in 10^5. Other calculations on unpolarized 50–500 eV electrons scattered from optically active 1,3-dimethylallene showed an asymmetry < 1 part in 2×10^6 (154). An experimental investigation of such stereoselective electron scattering was recently undertaken by Campbell and Farago (155), who measured the spin dependence of the scattering of polarized electrons by molecules of optical isomers in the vapor phase. When a 5-eV beam of polarized electrons was scattered by vaporized D- or L-camphor, the beam was attenuated with a (+) asymmetry by the L-camphor and a (−) asymmetry by the D-camphor. Thus "spin polarized electrons, like polarized light, when scattered from optically active molecules, can 'distinguish' between right-handed and left-handed isomers."

b. Protons and Muons. In an extension of experiments testing the V–U hypothesis, Lemmon and co-workers (139) undertook the irradiation of DL-leucine with longitudinally polarized protons of both P and AP spin. These were produced in an 88-in. sector-focused cyclotron, which gave a 10–14 nanoampere beam of protons having ~80% net polarization and energies ranging from 0 to 10 MeV. It was anticipated that such proton experiments might have certain advantages over the previous polarized electron irradiations: (1) the proton beam had a higher net polarization than was available with the earlier electron beams; (2) the proton, with a mass over 1800 times that of the electron, has only ~2.2% of the velocity of an electron of the same kinetic energy, such that the slower velocity of the proton might maximize the time for interaction between the polarized protons and the electrons of an optically active substrate; and (3) the ionization density along a proton's track will be much greater than that along the track of the much lighter electron.

Three irradiations were conducted with P and three with AP spin protons. Increasing doses from 1 to 9×10^8 rads were used, affording from 7 to 50% gross degradation. Each irradiation was conducted with two samples in tandem. In the first the proton beam passed through the sample, and in the second the proton beam was stopped completely by the sample. The irradiated samples were then recovered and their enantiomeric compositions were determined in the usual way by analytical GC. All of the irradiated DL-leucine samples still proved to be racemic within experimental error, indicating no stereoselectivity during the degradations.

In addition to the potential advantages enumerated above for using protons in such experiments, there is also a disadvantage. The magnetic moment of the proton is only about 1.5×10^{-3} that of the electron. Thus the spin–spin interaction between the polarized proton or electron, on the one hand, and the electrons of a chiral molecule, on the other, would be much smaller in the case of the proton. It was suggested (139) that this disadvantage might negate the abovementioned advantages of using polarized protons.

In a later study (140) the possibility of radioracemization by protons was also investigated. The D- and L-leucine samples were subjected to 39–55% radiolysis using 0–11 MeV protons produced as above, again with both the beam passing completely through the sample or being totally stopped by it. The irradiated samples were quenched and analyzed by GC immediately upon completion of the irradiation, or after a 21-day period. Racemization proved to be very slight (1.1–1.7%) and was comparable in all the experiments, suggesting that radioracemization and secondary degradative effects were not important factors in the previous unsuccessful attempts to induce optical activity in DL-leucine by partial radiolysis using 0–11 MeV longitudinally polarized protons.

The positive muon (μ^+) has a mass about one-ninth that of the proton and is formed, along with a neutrino, in the parity-violating decay of a positive pion (π^+) (eq. [1]). This process, which is a rare one occurring in cosmic pion decay, can be duplicated artificially in the laboratory. The μ^+, which is ~100% longitudinally polarized and has an intrinsic lifetime of 2.2×10^{-6} secs, decays by forming a positron (e^+) and two neutrinos (eq. [2]) (136).

$$\pi^+ \rightarrow \mu^+ + \nu_\mu \qquad [1]$$

$$\mu^+ \rightarrow \varepsilon^+ + \nu_e + \bar{\nu}_\mu \qquad [2]$$

When the μ^+ is slowed down and stopped on entering matter it may capture an electron to form a neutral, hydrogen-like atom of "muonium" (μ^+e^-, Mu). Since the μ^+ is initially spin-polarized, the Mu may exist in two states, depending on the spin of the captured electron, a "triplet" state in which the spins of the μ^+ and the e^- are parallel or a "singlet" state in which the spins are antiparallel. Because of the high degree of polarization of μ^+, the formation of Mu or its subsequent chemical reactions might vary between optical isomers, and since polarized μ^+ is among the components of cosmic rays, such a stereoselective interaction of μ^+ with racemic matter might provide another determinate mechanism for the abiotic origin of molecular chirality.

Lemmon and co-workers addressed this possibility experimentally in 1974 (141) by irradiating crystalline D- and L-alanine and liquid D- and L-2-octanol with μ^+ beams produced in a 184-in. cyclotron at the Lawrence Berkeley Laboratory. They then measured the "residual polarization" and the "residual asymmetry" of the μ^+ after entering the enantiomeric targets. No differences beyond experimental error were found in either pair of enantiomers, and the authors concluded that there was "no significant difference between the reaction probabilities of polarized Mu atoms with enantiomers of alanine and 2-octanol."

Another attempt to assess the possible stereoselective effect of longitudinally polarized muons was made by Spencer and co-workers (142) 5 years later. They conducted careful measurements of the amount of "triplet" Mu formed by irradiating *d*-quartz and *l*-quartz with μ^+ beams in a transverse magnetic field, in an effort to see whether Mu formation was sensitive to the chirality of the stopping medium. Their findings were that the amount of Mu formed did *not* depend on the chirality of the quartz sample to an accuracy of 1%.

c. **Positrons.** The positron e^+, the positively charged counterpart of the electron, is emitted with high kinetic energy ($\sim 10^3$ keV) during the radioactive decay of neutron-deficient nuclides such as ^{22}Na and, because of parity violation during the decay, with a predominantly "right-handed," P-spin longitudinal polarization (136). Positrons begin to lose their high kinetic energy within $\sim 10^{-12}$ sec on colliding with surrounding matter. On reaching thermal or near thermal energies (~ 10 eV), a large fraction of them annihilate directly on collision with the electrons of the matter, producing two γ-ray photons for each annihilation, a process taking $\sim 2 \times 10^{-10}$ sec. A smaller fraction of these low-energy positrons may combine with the electrons to enter the bound state of "positronium" (e^+e^-, Ps). The fraction of e^+ that converts to Ps, as opposed to annihilating directly, varies with the chemical and physical properties of the medium (136). Just as with muonium, Ps may exist in two ground states, a "triplet" or "ortho" state (o-Ps) in which the spins of the e^+ and e^- are parallel, or a "singlet" or "para" state (p-Ps) having the spins antiparallel. Both o-Ps and p-Ps are intrinsically unstable. Free p-Ps, with a mean lifetime of 1.25×10^{-10} sec, annihilates into two 0.51 MeV γ-ray photons, while the longer-lived o-Ps, whose mean lifetime is 1.4×10^{-7} sec, annihilates into three γ-photons (143). Positrons emitted during radioactive decay are believed to partially maintain their longitudinal polarization during their deceleration and conversion to Ps in matter (144).

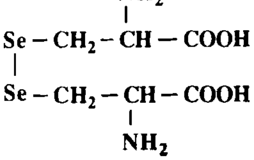
In an attempt to avoid some of the factors that might have prevented the observation of any stereoselective degradation of enantiomers by longitudinally polarized electrons in earlier experiments where only the products of the interactions were examined, Garay and co-workers in 1973 (144) initiated a study of the annihilation of positrons by optical isomers, hoping that this technique might give "information about the interaction process itself rather than about the products of interaction." The D- and L-enantiomers of tryptophan, phenylalanine, tyrosine, and dihydroxyphenylalanine were individually packed around a $\sim$0.8-μCi ^{22}Na positron source and placed between two scintillation counters, whereupon the "lifetime spectrum" of each sample was measured. It was found that the intensity of the long-lived triplet o-Ps diminished in the order tryptophan > phenylalanine > tyrosine

>dihydroxyphenylalanine, that the triplet intensities in the D-amino acids were higher than those in the corresponding L-enantiomers, and that triplet lifetimes were also different in each of the pairs. The results were interpreted as indicating that there was a difference in the relative probabilities of o-Ps and p-Ps formation for the enantiomers in each pair, although the possibility was not excluded that the differences were caused by "some unknown difference in the materials" (144).

The first attempts to repeat Garay's observations on the stereoselective annihilation of positrons by amino acid enantiomers was that of Dezsi and co-workers in 1974 (145), who likewise irradiated eight different enantiomeric pairs of amino acids with positrons from ^{22}Na. Slight differences in the intensities of the long-lived component of the lifetime spectra were noted, but since the sign of these differences varied from one enantiomeric pair to another, the authors were at a loss to explain their data. A year later Brandt and Chiba (146) attempted high-precision measurements of the lifetime spectra of a number of samples of D- and L-tryptophan from several different sources. They found no differences whatsoever in the lifetimes or intensities of any of the spectral components in any of their samples.

Garay's results and his interpretation that the "D-isomers of amino acids favor triplet states in the case of forward polarized β^+ particles" (144) were immediately questioned on theoretical grounds by Rich (147), who argued that positrons should lose their helicity before Ps formation is possible and suggested that the observed effects, if valid, were due to an "undetected chemical impurity" or to "some slight difference between the solid state structure of the L and D crystals" in the system. The correctness of these criticisms was established experimentally a year later by Jean and Ache (143, 148) who performed positron lifetime spectra measurements on the optical isomers of six carefully purified chiral organic compounds, including the D-, L-, and/or DL-enantiomers of 2-methylbutanol, 2-aminobutanol, 2-octanol, α-methylbenzylamine, carvone, and ethyl tartrate. Experiments were conducted at from four to seven different temperatures ranging from -196 to $+100$°C. No significant differences in the lifetimes or intensities associated with either the short- or long-lived components of the positron lifetime spectra were observed between the D- and L-enantiomers of the compounds studied when the experiments were done in the *liquid* state. The results thus provided no evidence for the assumption that enantiomers display different cross sections for o-Ps formation and cast doubt on "the predictions of previously proposed models for the interaction of longitudinally polarized positrons with the spin polarized electrons in chiral molecules." Suggested reasons for the discrepancy were the invalidity of the assumption that electrons in chiral molecules possess a helicity when they form Ps with positrons, or the assumption that positrons retain their longitudinal polarization on slowing down until they form Ps. Some differences in the intensities of long-lived components in the positron lifetime spectra were noted when enantiomers were studied as frozen solid samples. Such differences were attributed to variations in the phase or crystal structures, and not to different helical electronic structures of the enantiomers.

In attempts to circumvent some of the experimental difficulties inherent in earlier studies of stereoselective positron annihilation by enantiomers, Gidley et al. (149) recently described a new apparatus for the production of polarized positrons. This technique has the advantages that (1) a low-energy positron beam is produced, which preserves much of the helicity of the positron, which was lost in previous experiments; (2) the helicity of the e^+ is reversible during the experiment, providing for both a "symmetry check" and a measurement of any asymmetry without the need to change enantiomers; and (3) a potential sensitivity increase is possible, by a factor of $\sim 10^4$. These investigators then employed this equipment (150) to measure A_{Ps}, the asymmetry of triplet o-Ps formation, observed either on reversal of positron helicity (P or AP spin) or target chirality (D or L), for the D-, L-, and DL-forms of cystine, tryptophan, and leucine. The measured values of A_{Ps} showed no statistically significant difference between the D and L enantiomers of cystine or tryptophan at the 7×10^{-4} level. However, a nondefinitive but possible effect of $31 \pm 7 \times 10^{-4}$ was found for leucine enantiomers. Later the asymmetries for D-, L- and DL-leucine were again measured (151), using an improved apparatus which produced positron beams of higher intensity and polarization and had greater sensitivity, with the finding that the L versus D asymmetry for leucine was $A_{Ps} = 0.8 \pm 1.0 \times 10^{-4}$, a value consistent with a null result to 1 part in 10^4. These data were then used to calculate the maximum experimentally observable asymmetry in the stereoselective β-radiolysis of DL-leucine as $< 5 \times 10^{-9}$. Since A_{Ps} is proportional to Z^2, the square of the atomic number of the dominant heavy atom in the chiral environment of the target molecule (152), later attempts were made to determine whether larger asymmetry values might be observed if elements having Z larger than that of carbon ($Z = 6$) were employed in the targets. For these experiments selenocystine ($Z = 34$), **49**, and thyroxine ($Z = 53$), **50**, were employed. The A_{Ps} values were $(5.2 \pm 3.3) \times 10^{-4}$ for **49** and $(1.9 \pm 3.6) \times 10^{-4}$ for **50**, respectively, both



$$\begin{array}{l}Se-CH_2-\overset{NH_2}{\overset{|}{C}H}-COOH\\ |\\ Se-CH_2-\underset{NH_2}{\underset{|}{C}H}-COOH\end{array}$$

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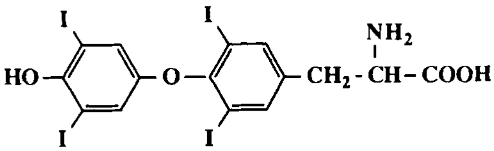

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values being consistent with a null result (152). Future experiments using more sensitive measurements on molecules containing higher Z elements were contemplated to see if a nonzero value of A_{P_s} might be observed (152).

4. *Parity Violation and the Properties of Enantiomers*

In Sect. III-B-1-3 we examined experimental efforts to detect stereoselective interactions between enantiomers and various longitudinally polarized, chiral, subatomic particles produced as a consequence of parity violation during the decay of certain radioactive nuclides. The possible intervention of parity violation in the development of an enantiomerically homogeneous biosphere is not limited, however, solely to the external effects of such chiral particles on enantiomers. On a more fundamental level, parity violation is believed to influence the essential properties of enantiomeric molecules themselves, making them intrinsically disposed toward manifesting stereoselective effects in their reactions, either with themselves or with other molecules. In this section we shall examine briefly the numerous theoretical and occasionally experimental studies which have been reported along these lines.

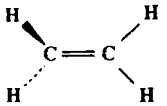
a. Weak Interactions, Neutral Currents, and Energy Differences. Subatomic particles fall into three classes: photons, leptons, and hadrons (156). The lepton class includes electrons (e^-), positrons (e^+), (+) and (−) muons, (+) and (−) tauons, and neutrinos and antineutrians (136). The hadron class includes mesons and baryons (156). Such particles are also classified according to their spin as bosons (spin $= \pm 1$) or fermions (spin $= \pm\frac{1}{2}$). These subatomic particles interact with each other in one or more of four different ways: by strong (or hadronic interactions (SI), by electromagnetic interactions (EMI), by weak interactions (WI), and by gravity (G). The relative strengths of these interactions vary enormously, as seen in the following ratios: $\mathrm{SI}:\mathrm{EMI}:\mathrm{WI}:\mathrm{G} \approx 1: \sim 10^{-2}: 10^{-5}: 10^{-40}$ (157, 158). The EMIs and G act over infinite distances, while the SIs and WIs require the incredibly short ranges of 10^{-13} to 10^{-14} and $\leqslant 10^{-14}$ cm, respectively, for their operation (157). The SIs hold the protons and neutrons together in atomic nuclei, while the EMIs determine how electrons move in their orbits around atomic nuclei. Thus the EMIs are important when atoms combine in molecules by ionic or covalent bonds, and when molecules combine as polymers or aggregates linked by covalent bonds, H-bonds, and electrostatic or van der Waals forces. In short, the EMIs are dominant in chemistry and biology. The various interactions are believed to be "mediated" by other particles, that is, a current of the mediating particle "flows" between the interacting species. Thus in EMIs a photon is the mediating particle exchanged between the interacting species. In the WIs the mediating particles are thought to be charged or neutral bosons ($W^{\pm}$ or Z^0), and their exchanges are referred to as "charged currents" or "neutral currents," respectively (156, 159). The existence of such neutral currents has been recently verified by several types of experiment (159).

Parity is conserved in SIs and EMIs, and was assumed also to be conserved in WIs until 1956, when Lee and Yang predicted that parity was actually violated in the WI involved in β-decay (Sect. III-B-1). Parity is now thought to be violated in all of the WIs. Parity nonconservation in the charged current WIs, resulting in spin polarized electrons or positrons, as discussed above, has little effect in ordinary atomic or molecular processes (159). In contrast to the charged current WIs, however, the neutral current interactions may produce observable effects in ordinary atomic or molecular processes, resulting in weak distortions of virtually all electromagnetic effects (159). In particular, the neutral currents have been predicted to require that there be an *energy difference* between enantiomers. Thus the total energy of an L enantiomer will not be equal to that of a D enantiomer. Rather, because of the neutral current WI, the energy of the L enantiomer will be $E(\text{L}) = E(1+\varepsilon)$ and that of the D isomer $E(\text{D}) = E(1-\varepsilon)$, where E is the energy of either enantiomer in the absence of the neutral current effect (156, 159). The difference, $\Delta E = 2\varepsilon$, which can vary widely from one type of molecule to another (159), is referred to (165) as the parity-violating energy difference (PVED) between the two enantiomers. It is believed to have potentially profound consequences for the two enantiomers and, as we shall see below, has been causally implicated by many authors in the origin of our present biomolecular homochirality.

The reason for the existence of a PVED is that the "parity nonconserving weak neutral current interaction and the usual spin–orbit interaction act together to produce a small energy shift in a handed molecule," a shift equal in magnitude but opposite in sign in enantiomers (159). The development of these concepts and conclusions is based on sophisticated quantum mechanical arguments which require a specialized background for their full appreciation. An equally fundamental but intuitively (for the nonspecialist) more understandable basis for PVEDs has recently been described by L. D. Barron of Glasgow (160). Based on considerations of the basic symmetry operations of parity (space inversion), time reversal, and charge conjugation, Barron defines the difference between "true" and "false" chirality, and points out that D and L enantiomers are really not "true" enantiomers, since they represent merely space-inverted structures which have not also undergone charge reversal. A true enantiomer would be a chiral molecule having not only the opposite absolute configuration but also composed of *antimatter* particles. Such a pair of true D-matter and L-antimatter enantiomers would be strictly degenerate and would have precisely identical energies. Since terrestrial D-matter and L-matter enantiomers are thus not strictly degenerate, there must be a small energy difference between them, the PVED. It is amusing to contemplate that a true D-matter, L-antimatter racemate could not exist, since the matter and antimatter enantiomeric components would annihilate each other to form γ-ray photons.

b. Theoretical and Experimental Consequences. The magnitude of the PVEDs between enantiomers has been an item of considerable interest to a number of investigators, particularly as it concerns the questions of whether the PVEDs are large enough to overcome "statistical fluctuations," whether small PVEDs might "tip the balance" at the critical point in spontaneous bifurcation processes, and whether PVED or β-decay is the most viable parity violation hypothesis for the origin of molecular chirality.

In 1974 D. W. Rein was apparently the first to make a theoretical calculation of the magnitude of the PVED, concluding that the energy difference between enantiomers, expressed as $\Delta E/E$, was $<10^{-10}$, and possibly even "smaller by orders of magnitude" (161). A year later Letokhov (162) estimated that differences in the energy levels of the molecular spectra of enantiomers on the order of 10^{-16} should exist, and boldly extrapolated that such small 10^{-16} differences in the reaction rates of enantiomers would be "quite sufficient for full selection of either of two stereoisomeric forms of all the amino acids that occur in the animate nature" in the 10^8–10^9 years during which self-replicating organisms developed. No mechanism for this miracle was suggested. In 1979 Rein and co-workers (159, 163) estimated the PVED for two chiral molecules, ethylene with a 10° out-of-plane twist (**51**) and the dialkyl sulfide, A-nor-2-thiacholestane (**52**). The PVED for **51** was calculated to be $\sim 10^{-18}$ eV, while that of **52** was $\sim 10^{-20}$ eV. Mason and Tranter in 1983 (164) were the first to calculate the PVEDs for amino acid enantiomers. The energy shift was found to depend both in sign and magnitude upon the particular conformation of the enantiomers. L-Alanine in an assumed "preferred conformation" in aqueous solution was calculated to have a ground-state energy lower than that of D-alanine by $\sim 1.6 \times 10^{-18}$ eV. Similarly, L polypeptides in the α-helix or β-sheet conformations were estimated to have lower energies than D polypeptides by $\sim 8 \times 10^{-20}$ eV for each peptide unit in



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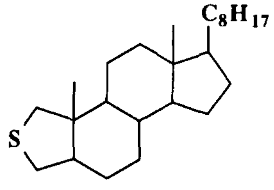

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the chain. Such small energy differences were considered "to require amplification mechanisms or a dynamic metastable system sensitive to small perturbations" to provide observable consequences of the PVEDs. Similar calculations were later extended by Tranter (165) to glycine, alanine, valine, serine, and aspartic acid, again in their assumed "preferred conformations" in aqueous solution. The L enantiomers were once again found to have lower ground state energies by ~ 2 to 5×10^{-19} eV. Taken as a free energy difference, such PVEDs correspond to an enantiomeric excess of ~ 1 part in 10^{17} for L enantiomers in racemic mixtures in thermodynamic equilibrium at normal terrestrial surface temperatures (165). Realistically, this is an incredibly small number. It corresponds, for example, to one star out of all the stars in a million of our galaxies. Nevertheless, it is concluded, "with no absolute proof," that the "results reported here provide evidence that the observed terrestrial homochiral biochemistry had its origin" in the small PVEDs between enantiomers (165).

Not all authors, however, have been so optimistic about the direct implication of PVEDs in the origin of chirality. Thus, after making their calculations for structures **51** and **52**, Rein and co-workers (163) concluded that PVEDs between enantiomers "of the order of 10^{-18} eV and below might hardly be taken to be responsible for the ultimate optical asymmetry through which life is thought to have evolved." In his recent review on parity violation as a source of chirality, Keszthelyi (166) closes by stating that "it may be safely concluded that small asymmetries caused by parity violation do not induce optical purity."

A number of authors have considered the question of which parity violating effect, PVEDs or β-decay, might be most effective for the origin of chirality. The question, of course, can be addressed only theoretically. To do so, the authors generally have had to make a number of quite arbitrary assumptions about the conditions on the primitive Earth at the time when the effects might have been operative. These assumptions have involved a wide variety of factors, such as the types, amounts, energy ranges, distributions, and concentrations of the β-decaying nuclides available, the duration of their action (exposure times), the prevailing temperatures, and the possibilities of racemization. In 1976 Keszthelyi (128) concluded that an asymmetry in the population of amino acids due to β-radiolysis could survive racemization, even when the asymmetry was as low as $\sim 10^{-5}$. Fajszi and Czege (167) improved on Keszthelyi's model and found that for large cross sections for the β-ray interactions the β-radiolysis effect should prevail over statistical fluctuations, while Mann and Primakoff (168) also calculated that β-decay processes might produce a steady-state net chirality in the prebiotic era. On the basis of results obtained in triplet-positronium formation experiments (150), Hegstrom has computed (169) that the asymmetry for the β-radiolysis of amino acids is

10^{-11}–10^{-12} with 100 keV electrons, while the asymmetry for PVED effects is $\sim 10^{-17}$ (165, 171). Finally, Hegstrom and co-workers have calculated (170, 171) that the asymmetries produced by β-decay from a variety of natural sources should be greater than that produced by PVED effects at lower temperatures, while PVED effects should dominate at higher temperatures, but with the production of smaller asymmetries.

In 1966 Yamagata (172) proposed a novel process whereby reaction rate differences between enantiomers resulting from small PVEDs might result in large chiral excesses through an "accumulation principle" operating during a polymerization reaction. To paraphrase, he assumed that the buildup of a biopolymer containing n monomer units of identical chirality may, because of the PVED, proceed with different rates for D and L enantiomers. If $p = k_D/k_L$, the rate ratio for each step in the polymerization, and if $p \approx 1$, but is actually slightly greater than 1 (ie., $1+\varepsilon$) owing to the PVED, then the ratio of L to D molecules after n steps is given by eq. [3].

$$\frac{N_L}{N_D} = p_1 p_2 p_3 \ldots p_n \approx p^n = (1+\varepsilon)^n = \exp \varepsilon n \qquad [3]$$

Postulating that $\varepsilon \approx 10^{-7}$ and $n \approx 10^8$, Yamagata then concluded that such a cumulative processes could lead to an essentially chirally pure biopolymer. Ignoring the stereochemical difficulties inherent in such a process, Morozov and co-workers (173) have recently pointed out that any such scheme assumes that the initial state of the system is totally racemic. Because of statistical fluctuations (Sect. III-A-1), however, this is never the case. A real estimate of the effect of PVEDs on chiral symmetry breaking can be made only if the competing role of statistical fluctuations is taken into account (173). The authors then attempted to take these considerations into account, and they are also implicit in more recent theoretical studies.

In 1982 Liu (174) was apparently the first to develop a mathematical model in which an external "asymmetric agent" plays a selection role near the "bifurcation point" of an autocatalytic symmetry breaking system of chiral antipodes (Sect. III-A-1), thus forcing the system into a given, nonrandom path. The initial asymmetry is subsequently amplified to the extent that it becomes irreversible, resulting in the production of only one enantiomer. No specific external agent was proposed, but several were suggested, including parity nonconservation in the weak interactions.

A year later Kondepudi and Nelson (175) independently developed such ideas further for nonequilibrium chemical systems. They considered the synthesis of a chiral molecule which could give either a D or L product in the absence of a chiral influence. If such a system has appropriate autocatalytic or cross-catalytic kinetics and is far from equilibrium, there can arise a critical bifurcation point beyond which the system is dominated by either the D or the

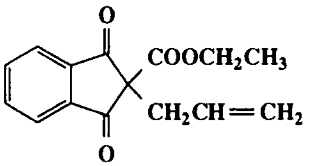
L enantiomer, although their kinetics are the same. They then showed that such systems are extremely sensitive to small external chiral interactions, and that interaction energies on the order of $\Delta E \approx (10^{-17}$ to $10^{-15})kT$, where kT is the thermal energy, are sufficient to produce good chiral selectivity in reasonable times. They then pointed out that since the PVEDs are in the neighborhood of $\sim 10^{-15}$ to 10^{-11} kT, depending on the atomic number Z at the chiral center, they are of a sufficient magnitude to provide the external chiral influence affecting such a system at its bifurcation point. For other conceivable external chiral interactions (such as combinations of electric, magnetic, gravitational, or centrifugal fields), they estimated that ΔE would be orders of magnitude smaller (i.e., 10^{-19} kT). They thereupon concluded that "weak neutral current effects though extremely small, are large compared to other chiral interactions at the molecular level, and in fact are large enough to produce observable effects of selection in an appropriate chemical system." The influence of small chiral disturbances acting at the bifurcation point to produce a net chirality in mathematically modeled systems has been discussed by others (176) and reviewed in detail on several recent occasions (164, 177).

In 1985 Hegstrom (178), on the basis of new estimates on the asymmetric radiolysis of racemates by β-radiation (171) and on his own redefinitions of the chiral selection parameters in the Kondepudi–Nelson scheme (175), calculated that in symmetry-breaking autocatalytic reactions of the sort proposed by Kondepudi and Nelson the chiral selection due to β-radiolysis may be a million times larger than that produced by PVEDs in the enantiomers. He therefore concluded that "β-radiolysis is more likely to be the selector of biomolecular chirality than weak neutral currents." Tranter (179), however, has recently modified the PVED symmetry-breaking hypothesis to include the possible additional transfer of the effects of mineral catalysts such as quartz or clays. These were assumed to have PVED-generated enantiomeric excesses in their crystal lattices, which might be greater than those possible in individual molecules, and hence more able to induce ultimate stereoselective effects. Again, there is absolutely no experimental basis for such PVED-generated processes leading to chiral mineral catalysts.

Unfortunately, no new experiments were conducted by the various authors to support any of the plethora of conflicting theoretical conclusions outlined above and, in fact, few experiments were even suggested. Several experimental observations have been reported by others, however, which may have a bearing on the subject of PVEDs. In 1970 Thiemann and Wagener (180) studied the fractional precipitation of sodium ammonium DL-tartrate and found optical rotations of ~0.001° in a number of the final products. Having tested for and eliminated all artifactitious explanations, the authors concluded that the effect was due to differences in the lattice energies of the enantiomorphic crystals. A short time later Yamagata (181) proposed a refinement of such experiments, and Wagener (182) suggested other observable physical processes which might be sensitive to energy differences between enantiomers. Keszthelyi (183) has used the stereoselective crystallization data obtained by Kovacs and Garay (129) for sodium ammonium DL-tartrate to calculate an energy difference of $\sim 10^{-10}$ eV between the two enantiomers. One of the more interesting experimental manifestations of a possible PVED effect was the observation of Merwitz (184) in 1976 that solid-state samples of D-, L-, and DL-phenylalanine underwent decarboxylation by nonpolarized γ-radiation at different rates. Using ^{14}C-labeled starting materials, he found that for irradiations in the 10^2–10^4 rad dose range the decarboxylation rate for D-phenylalanine was as much as 2.7 times greater than that of the L enantiomer, while the rate of DL-phenylalanine fell half-way in between. He thereupon suggested that the results were due to small energy differences in the enantiomers which were amplified by a cascading effect in the radiation-induced solid-state chain reactions. These remarkable observations were subsequently extended and confirmed in 1985 by Norden and coworkers (185) using leucine enantiomers. They also suggested that the effects could be due to the fundamental PVEDs between the enantiomers, although the possible intervention of more mundane causes, such as impurities or crystal defects in the samples, could not be excluded. Garay (186) has interpreted the results of Merwitz as caused by differences in the "internal timing" between D and L enantiomers, brought about by different "helicities" of the electron systems in the enantiomers. So far no other theoreticians have commented on these novel suggestions.

5. *Electric, Magnetic, and Gravitational Fields*

Pasteur was probably the first scientist to study the question of the origin of enantiomeric bias experimentally, having conducted numerous experiments in the presence of magnetic fields, rapidly rotating tubes, reversed diurnal illumination, and the like. Such experiments were uniformly unsuccessful, as were similar ones subsequently conducted by others (3). The first positive report of a stereoselective synthesis conducted in the presence of a magnetic field was that of Radulescu and Moga (187) in 1939, who treated 2-allyl-2-carbethoxy-1,3-indandione (**53**) with HBr and Br_2 between the poles of a powerful magnet and under intense illumination with polarized light. The spiran-type products **54** and **55**, respectively, were reported to show a slight optical activity, but "the results were disappointing". Some 28 years later Pracejus (188) attempted to repeat Radulescu's asymmetric synthesis of **54** and **55** in a magnetic field, but was unable to do so. A second positive report appeared in 1975, when Gerike (189) carried out six chemical reactions



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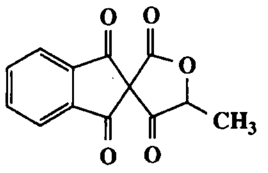

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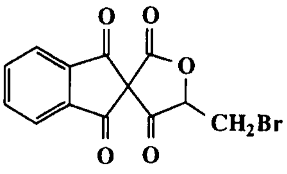
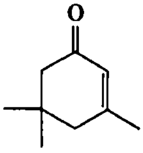


55

leading potentially to optically active products under the combined influences of electric and magnetic fields arranged in a variety of configurations. The reactions included the epoxidation of isophorone (**56**) to its epoxide (**57**) with H_2O_2, the polymerization of methyl methacrylate (**58**) with peracetic acid, the bromination of methyl acrylate and **58** in $CHCl_3$, and the reactions of 2-butanone with benzylmagnesium and phenylmagnesium halides to



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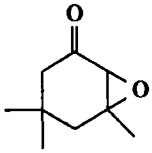

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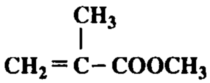
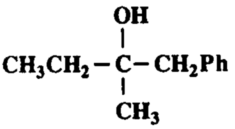


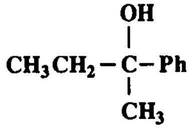
$$CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}COOCH_3$$

58



$$CH_3CH_2{-}\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{C}}{-}CH_2Ph$$

59



$$CH_3CH_2{-}\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{C}}{-}Ph$$

60

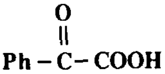
produce the tertiary alcohols **59** and **60**, respectively. The optical rotations of the products, measured polarimetrically at four different wavelengths, proved to be randomly either (+) or (−), and of a magnitude ~0.001–0.032°. It was not long until the claims of Gerike were disputed on theoretical grounds. In 1977 Mead et al. (190) argued on the grounds of symmetry and time-reversal operations that no combination of uniform and constant electric (E) and magnetic (H) fields could lead to stereoselective reactions with initially racemic or symmetrical molecules, and suggested that whatever the source of the rotations in Gerike's products, they could not have had their origin in the uniform applied fields if the reactions had gone to completion. These criticisms initiated a series of polemical discussions which continues to this day. A year later Rhodes and Dougherty (191) pointed out that the Mead–Moscowitz arguments were valid only under conditions of complete thermodynamic equilibrium, and did not apply to kinetically controlled reactions which can reach completion before thermodynamic equilibrium has been established. They showed that constant, uniform, and parallel E and H fields can selectively affect the rate constants for the formation of two enantiomeric products if a magnetic moment exists in the transition states leading to the enantiomers. Assuming certain values for the transition state parameters, they calculated that the effect would be quite small, however, with enantiomeric excesses of ~0.3 ppm resulting at 298°K with fields of $E = 10^3$ V/cm and $H = 10^4$ G.

A short time later Dougherty and his collaborators made a series of further controversial claims for successful asymmetric syntheses, this time under the influences of gravitational fields (192). They again studied the epoxidation of **56** to **57**, but now in the gravitational field of a confined vortex. The reactions were conducted in rapidly spinning tubes (~ 12,000 rpm) which could be spun clockwise or counterclockise in either horizontal or vertical configurations. The product **57** was then examined polarimetrically and, depending on the experimental configuration, optical rotations of -0.0031 to $+0.0172°$ at 546.1 nm were obtained, values "well beyond experimental error." Differences in the results for different experimental configurations were explained as due to combinations of gravitational and coriolis forces, and the results were claimed to "demonstrate that it is possible to obtain asymmetric synthesis with chiral gravitational fields alone." The suggestion was also made that "prebiotic organic syntheses could have been partially asymmetric" as a result of such gravitational field effects. Dougherty later extended such studies (193) to these and other organic reactions conducted now under the influence of magnetic fields which could be reversed with respect to the earth's geometric axis. The optical rotations of the products, all in the ± 0.0002 to $0.0074°$ range, were found to vary capriciously with the orientation of the field, the time of day, and the date, while appropriate "bench controls" showed no optical rotations.

These claims were no sooner made than they were vigorously refuted by Mead and Moscowitz (194) who, again on detailed theoretical grounds, concluded that the theoretical points made by Dougherty and co-workers were "entirely without foundation and cannot possibly be taken seriously as an explanation for the data reported," and that "the most likely explanation by far is that they are due to some artifact." Peres (195) also criticized Dougherty's results because they violate "the gravitational analogue of de Gennes' theorem on the impossibility of asymmetric synthesis in a static electromagnetic field." Somewhat similar experiments were conducted later by Kovacs and co-workers (196), who conducted polymerization experiments on γ-benzyl DL-glutamate *N*-carboxyanhydride (**86**) solutions while stirring them rapidly in clockwise or counterclockwise directions, as well as crystallization experiments of sodium ammonium DL-tartrate from similarly stirred solutions. The resulting products were examined for effects of stereoselectivity, but the results were quite inconclusive. Similarly, the reported production of a slight enantiomeric excess induced by a conical swirl during the synthesis of a cyanine dye (197) was later attributed to artifactitious optical rotations caused by linear dichroism from accidentally oriented material (198). In his recent papers (160) describing the very useful concepts of "true chirality" (systems with "time-invariant" enantiomorphism) and "false chirality" (systems with "time noninvariant" enantiomorphism), Barron has analyzed these conflicting claims on the stereoselective effects of electric, magnetic, and gravitational fields, concluding that "only a truly chiral influence can induce absolute asymmetric synthesis in a reaction mixture which is isotropic in the absence of the influence and which has been allowed to reach thermodynamic equilibrium. But for reactions under kinetic control, false chirality might suffice." This would appear to agree with the conclusions of Dougherty's original arguments (191).

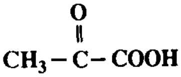
Several new suggestions have been made recently as to possible magnetic field influences which might lead to enantiomeric excesses. Thiemann (199), having noted some apparent anomalies in the magnetically induced circular dichroism (MCD) spectra of benzene and naphthalene, suggested that magnetic fields might generate chirality by rendering a prebiotic solvent optically active with MCD, so that a prochiral substrate might react stereoselectively in it. He then proposed an experiment (not yet conducted) to look for this effect. Wagniere and Meier (200) have theorized that in a static magnetic field parallel to the direction of propagation of an incident unpolarized light beam, there should be a small, equal, and opposite shift in the value of the absorption coefficients for D and L enantiomers. This magnetically induced absorption difference was then assumed to give rise to rate differences between the two enantiomers for photochemically mediated reactions, thus leading to stereoselective effects by "a new mechanism." In what would appear to be a closely related experimental study, Bernstein in 1972 (201) attempted the UV-mediated photochemical synthesis of hexahelicene (**17**) and several analogs in vessels oriented in different positions between the poles of a 65,000-G supercooled magnet. An ORD examination of the chromatographed products revealed no optical activity, and an upper limit of 0.02% was placed for any optical yield produced.

Finally, a remarkable experimental observation regarding magnetic field effects during electrolytic reductions has recently been reported. Takahashi and co-workers (202) conducted the electrolytic reductions at a mercury cathode of phenylglyoxylic (**61**) and pyruvic (**62**) acids to mandelic (**63**) and lactic (**64**) acids, respectively, at several pHs and in the presence of 980–1680 G magnetic fields having variable orientations with respect to the surface of the mercury cathode. The products were uniformly dextrorotatory when the magnetic flux was perpendicular to the mercury electrode surface, with the optical yield increasing proportionately to the magnetic flux density. No effect was observed with the magnetic field parallel to the electrode surface, and the effect was not reversed on interchanging the poles of the magnet. At 1680 G the polarimetrically measured optical yield of L(+)-**63** was 21%, and in the reduction of **62** the L enantiomer of **64** was also favored. The effect disappeared when the catholyte–cathode interface was disturbed by bubbling in a stream of nitrogen. Refreshingly, the authors admitted to being at a loss to explain their observations.



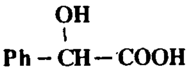
$\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}COOH}$

61



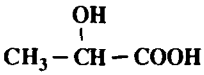
$\mathrm{CH_3{-}\overset{O}{\overset{\|}{C}}{-}COOH}$

62



$\mathrm{Ph{-}\overset{OH}{\overset{|}{CH}}{-}COOH}$

63



$\mathrm{CH_3{-}\overset{OH}{\overset{|}{CH}}{-}COOH}$

64

6. *Circularly Polarized Light*

Circularly polarized light (CPL) can be looked upon as an electromagnetic wave having its electric vector spiraling either clockwise (right-, or RCPL) or counterclockwise (left-, or LCPL) along its axis of propagation or, alternatively, as a photon which has either a forward (RCPL) or a reverse (LCPL) spin along its direction of travel. From either viewpoint, circularly polarized radiation constitutes a physical force characterized by "true" chirality (160), and thus has the potential capability of undergoing stereoselective, diastereomeric interactions with enantiomeric and prochiral molecular structures. Accordingly, well before the 1900s, LeBel (in 1874) (203) and Van't Hoff (in 1894) (204) suggested that CPL might be responsible for the origin of optically active molecules in nature. The numerous experimental attempts made to demonstrate such a phenomenon, dating from the turn of the century to the first successful results reported by Kuhn and co-workers in 1929–1930, have been extensively summarized elsewhere (3). Since Kuhn's era, processes involving CPL as the external chiral agent have proved to be the only determinate mechanisms for the origin of optical activity that have the twin capabilities of producing both readily observable and experimentally reproducible enantiomeric excesses, and the utilization of CPL has developed into a solid and substantial field of photochemistry.

All CPL-mediated reactions are initiated by the absorption of light by the reacting substrate (205) and depend ultimately on its circular dichroism ($\Delta\varepsilon = \varepsilon_R - \varepsilon_L$), that is, on the difference in the molar absorption coefficients, ε, for RCPL and LCPL for the enantiomeric or prochiral molecules of the substrate. The circular dichroism is greatest at the wavelength of maximum absorption for a critical chromophore in the substrate, so that CPL-mediated photochemical reactions are preferably conducted using radiation close to this wavelength. Since the rate of a photochemical reaction is proportional to the amount of the initiating light absorbed, the phenomenon of circular dichroism, where $\varepsilon_R \neq \varepsilon_L$, thus leads to different reaction rates for enantiomeric or prochiral reactants. Since $\Delta\varepsilon$ is (+) for one enantiomer and (−) to the same extent for the other, the practical consequence is that the interaction of CPL with enantiomeric or prochiral substrates results in a stereoselective reaction, with an equal and opposite bias, depending upon whether RCPL or LCPL is employed. An important quantity related to $\Delta\varepsilon$ is the "anisotropy factor" g, defined by Kuhn (206) in 1930 as $g = \Delta\varepsilon/\varepsilon$ (where $\varepsilon = (\varepsilon_R + \varepsilon_L)/2$), since g determines the "optical yield" or enantiomeric purity of the optically active product obtained.

Circularly polarized light-mediated asymmetric processes fall into three distinct categories: (a) partial photoresolution (optical activation, photoenantiomerization); (b) photochemical asymmetric synthesis; and (c) asymmetric photolysis (photodestruction) (205, 207, 208). In the remainder of this section we shall survey briefly the numerous experimental and theoretical investigations undertaken in each of these categories during the past several decades.

a. Partial Photoresolution. Partial photoresolution, or photoenantiomerization, consists solely of the photoequilibration of two enantiomers (eq. [4]) by CPL. The first-order rates for the forward and reverse reactions of the equilibrating system (eq. [4]) are given by eq. [5]. At equilibrium, the opposing rates are equal, so that eq. [6] applies. With ordinary light $k_D = k_L$, so that the equilibrium constant is $[\text{D}]/[\text{L}] = 1$. With CPL, however, since $\varepsilon_D \neq \varepsilon_L$ and since $k_D \propto \varepsilon_D$ and $k_L \propto \varepsilon_L$, then $k_D \neq k_L$ and at equilibrium eq. [7] applies. In other words, on irradiation with CPL the equilibrating system in eq. [4] approaches a steady state at which $[\text{D}] \neq [\text{L}]$, and the final equilibrium constant is determined by the ratio $\varepsilon_L/\varepsilon_D$. The optical yield for such a process, defined as the left-hand expression in eq. [8], is thus determined by the value of $g/2$ (205, 207). Unfortunately, g values for optically active compounds are rather small, on the order of 0.01 (205). Thus the optical yield, which increases in a partial photoresolution until the steady-state condition is reached, is limited to < 1% or so.

$$\mathrm{D} \underset{k_\mathrm{L}}{\overset{k_\mathrm{D}}{\rightleftharpoons}} \mathrm{L} \tag{4}$$

$$d[\mathrm{D}]/dt = -k_\mathrm{D}[\mathrm{D}]; \quad d[\mathrm{L}]/dt = -k_\mathrm{L}[\mathrm{L}] \tag{5}$$

$$k_\mathrm{D}[\mathrm{D}] = k_\mathrm{L}[\mathrm{L}]; \quad [\mathrm{D}]/[\mathrm{L}] = k_\mathrm{L}/k_\mathrm{D} \tag{6}$$

$$[\mathrm{D}]/[\mathrm{L}] = \varepsilon_\mathrm{L}/\varepsilon_\mathrm{D} \tag{7}$$

$$([\mathrm{D}]-[\mathrm{L}])/([\mathrm{D}]+[\mathrm{L}]) = (\varepsilon_\mathrm{L}-\varepsilon_\mathrm{D})/(\varepsilon_\mathrm{L}+\varepsilon_\mathrm{D}) = \Delta\varepsilon/2\varepsilon = g/2 \tag{8}$$

Partial photoresolutions were first described experimentally and theoretically by Stevenson and Verdieck in 1968 (209), who irradiated aqueous solutions of a number of racemic oxalato, malonato, and tartrato complexes of Cr^{+3} with CPL. The optical activity of the solutions increased positively with RCPL and, with perfect symmetry, negatively with LCPL as irradiation time increased, until equal and opposite steady-state optical rotation values were obtained. Stevenson later (210) used such photoenantiomerization reactions as a means of determining the circular dichroism of the substrates, and extended his studies to more complex systems in attempts to study the mechanism of the photoinversion process. During the same period several other investigators (211) studied similar photoenantiomerization systems, obtaining results generally similar to those reported by Stevenson and coworkers.

b. Photochemical Asymmetric Synthesis. Photochemical asymmetric synthesis refers to a process whereby an optically active product is formed from an optically inactive reactant in a photochemically mediated synthetic reaction brought about by CPL. Reactions in this category have been probably the most extensively studied of all CPL-induced processes. The generally accepted mechanism (205) for photochemical asymmetric synthesis is summarized in Figure 6. In this scheme a prochiral "D substrate" (an achiral

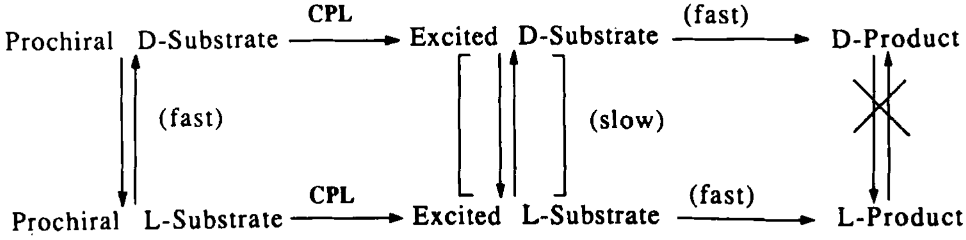


Figure 6. Photochemical asymmetric synthesis.

substrate existing in a particular chiral conformation) is in mobile equilibrium with a prochiral "L substrate" (having an enantiomeric conformation). The enantiomeric conformers are then activated by absorbing light to produce enantiomeric excited states, which may or may not be in slow equilibrium with one another. Finally, the excited states transform rapidly into enantiomeric products which are themselves incapable of photoequilibration. With ordinary light such a mechanism would clearly lead to equal quantities of D and L product. With CPL, however, the situation is different. Owing to the circular dichroism of the prochiral enantiomeric substrates, there is a differential absorption of CPL by each substrate, resulting in the formation of the two enantiomeric excited states at different rates and therefore in different concentrations. Since the excited states then convert rapidly into products, the mechanism clearly leads to the production of unequal amounts of each enantiomeric product. Thus RCPL should afford one particular enantiomeric excess in the product, while with LCPL under similar conditions the enantiomeric excess should be exactly equal and opposite.

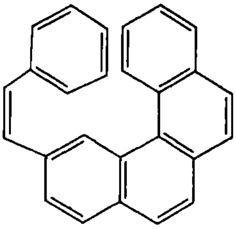
In photochemical asymmetric syntheses the optical yield is independent of the extent of completion of the reaction (207). The maximum optical yield obtainable is given by eq. [9] (205), where D-*S* and L-*S* refer to the enantiomeric prochiral substrate conformations. Thus we see that in photochemical asymmetric syntheses, as in partial photoresolution, the optical yield is again limited to $g/2$, or $< \sim 1\%$.

$$[\varepsilon_L(\mathrm{D}\text{-}S) - \varepsilon_L(\mathrm{L}\text{-}S)]/[\varepsilon_L(\mathrm{D}\text{-}S) + \varepsilon_L(\mathrm{L}\text{-}S)] =$$

$$[\varepsilon_L(\mathrm{D}\text{-}S) - \varepsilon_R(\mathrm{D}\text{-}S)]/[\varepsilon_L(\mathrm{D}\text{-}S) + \varepsilon_R(\mathrm{D}\text{-}S)] = \Delta\varepsilon/2\varepsilon = g/2 \qquad [9]$$

The first unequivocal photochemical asymmetric syntheses were reported in 1971 by Kagan and co-workers (213), who reported the photochemical ring closures with CPL (following by aromatization with I_2) of the 1,2-diarylethylenes 1-phenyl-2(2-benzo[c]phenanthryl)ethylene (**16**) and 1-(2-naphthyl)-2-(3-phenanthryl)ethylene (**65**) to produce hexahelicene (**17**). The **17** obtained from **65** had $[\alpha]^{23}_{436} = -30.0^\circ$ with RCPL and $+30.5^\circ$ with LCPL, while the **17** produced from **16** had -7.6° with RCPL and $+8.4^\circ$ with LCPL. The optical yields were thus low ($< \sim 0.2\%$), but the rotations were significant and reproducible. The authors also showed experimentally that the results could not have come from the initial production of DL-**17**, followed by a partial asymmetric photolysis. Such studies were subsequently extended (214) to the syntheses of octahelicene, $[\alpha]^{23}_{589} = -21^\circ$ with RCPL and $+20.2^\circ$ with LCPL, and of nonahelicene, $[\alpha]^{23}_{589} = +30.4^\circ$ with LCPL.

Quite independently and at the same time Calvin and co-workers were studying the identical photochemical asymmetric synthesis system (215).



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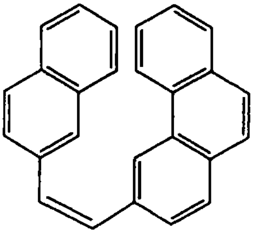

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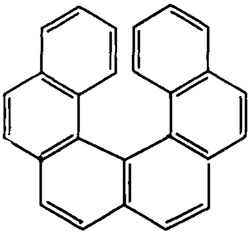
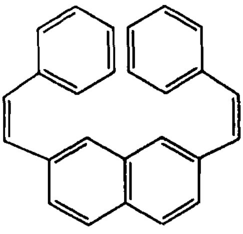


17

Starting with **16** or **65** and using the same reaction sequence they also produced **17**, as well as hepta-, octa-, and nonahelicenes from appropriate 1,2-diarylethylene precursors, finding again that RCPL gave levorotatory and LCPL dextrorotatory products. The photosynthesis of octahelicene was studied with LCPL at several wavelengths between 290 and 410 nm, with the finding that the optical yield of (+)-octahelicene increased steadily from −0.42% at 290 nm to ~ +2.0% at 410 nm. The authors considered three possible mechanisms to explain their data, finally choosing the one summarized in general terms in Figure 6 on the basis of a number of their experimental observations. The higher optical yield of **17** from **65** as opposed to **16** was rationalized in terms of more (in **65**) or less (in **16**) hindrance to free rotation in the photoexcited state intermediates. Such conclusions were subsequently refined by additional studies (205, 216) of helicene syntheses using diarylethylene precursors having ortho or para substituents in their aromatic rings.

Other photochemical ring-closure reactions besides those of simple diarylethylenes to produce helicenes have also been studied in attempts to produce asymmetric syntheses with CPL. In 1975 Kagan and co-workers (217) employed a series of bis(arylvinyl)arenes to produce a number of higher helicenes by a "double" photocyclization reaction. Their simplest examples consisted of the photocyclizations of the bis(arylvinyl)arene precursors **66** and **67** into hexahelicene, where it was found that both precursors produced



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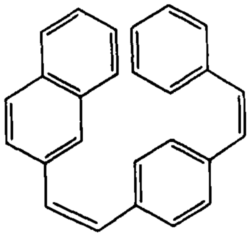
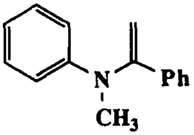


67

hexahelicene having $[\alpha]_{589} = +1.9°$ with LCPL. The optical yield was thus comparable to that previously obtained from **16**, suggesting that the latter was an intermediate in the double photocyclization. Shortly thereafter Nicoud and Kagan (218) described a new CPL-mediated asymmetric synthesis, preparing a series of *N*-methyl-2-aryldihydroindoles by the photocyclizations of *N*-methyl-*N*-arylenamines using 290–370 nm CPL. The prototype reaction was the synthesis of *N*-methyl-2-phenyldihydroindole (**23**) from the enamine precursor **22**, where the product **23** had $[\alpha]^{24}_{436} = -0.74°$ with



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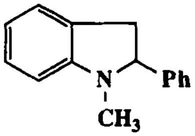
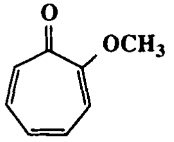


23

LCPL and +0.72° with RCPL. The optical yields were 0.2%, about the same as those found in the CPL photosyntheses of the helicenes. Finally, Zandomeneghi and co-workers in 1981 (219) irradiated 2-methoxytropone (**68**) with 350–356 nm CPL from a laser source, producing the ring-contracted



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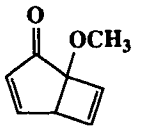
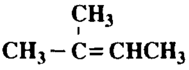


69

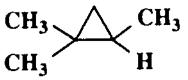
bicyclic dienone **69**. The crude solutions of **69** obtained after 130-min irradiation of **68** had positive or negative rotations of ~0.067°/dcm, depending on the handedness of the CPL employed.

Not all recent asymmetric photochemical synthetic attempts have been successful, however. In 1971 Boldt and co-workers (220) utilized CPL to generate carbenes photochemically from diazoalkanes, then added them to 2-methyl-2-butene (**70**) in attempts, for example, to generate an optically active form of 1,1,2-trimethylcyclopropane (**71**). Attempts were also made to form



$CH_3-\overset{CH_3}{\overset{|}{C}}=CHCH_3$

70



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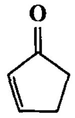

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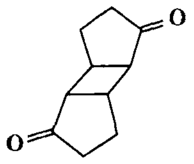


73

the optically active dimer **73** by the CPL induced photodimerization of cyclopentene-3-one (**72**). The results in all cases were uniformly negative, causing the investigators, at the early date of their report, to question whether asymmetric photochemical syntheses were in fact possible. Subsequent successful experiments, as indicated above, proved this gloomy prognostication to be inaccurate.

c. **Asymmetric Photolysis.** Asymmetric photolysis may be defined as the preferential destruction of one enantiomer over the other in a racemic mixture during photolytic destruction by CPL. Since the rate of a photolysis depends upon the amount of light of proper frequency absorbed by the substrate, and since, because of circular dichroism, the CPL of a given handedness will be absorbed unequally by the two enantiomers of a racemate, clearly there will be a difference in the rates at which the two enantiomers are destroyed (277). Thus if the photolysis is interrupted before completion, the unphotolyzed residue will be enriched in the enantiomer that had the lower ε and underwent photolysis more slowly. Asymmetric photolysis is unquestionably the most important of the three CPL processes from the viewpoint of the prebiotic origin of enantiomeric excesses. First, it is not limited to the rather specialized reaction systems for which partial photoresolution and photochemical asymmetric synthesis have been demonstrated, but rather is potentially applicable to any racemate whose molecules have chromophores absorbing at visible or UV wavelengths—that is, to the entire suite of racemic organic compounds. More important, the optical yield (enantiomeric excess) resulting in the unphotolyzed residue is not limited to a maximum of the mere ~1% imposed by the $g/2$ limit in the other CPL processes, but in principle can approach 100% if the g factor is high enough and the extent of photolysis is sufficient. In 1974 Kagan and co-workers (207) analyzed asymmetric photolytic systems theoretically and showed that the optical yields in the unphotolyzed residues are describable by a hyperbolic tangent function which increases continuously with time, so that enantiomeric purity approaches 100% as time approaches infinity. In this analysis they also provided a most useful table, abridged in Table 2, listing the enantiomeric purities obtainable as a function of extents of photolysis and the g values of the substrate and quantitatively illustrating the points made above.

Table 2
Enantiomeric Purity Obtainable During Asymmetric Photolysis

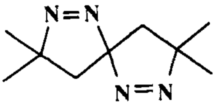
	g			
Extent of Reaction, (%)	0.02	0.24	1.00	1.50
20	0.22	2.68	11.44	17.75
40	0.51	6.15	26.73	43.00
60	0.92	11.02	48.07	77.37
80	1.61	19.30	77.60	99.20
99	4.60	51.63	99.92	>99.99

Kuhn's 1930 reports of the first successful CPL-mediated reactions (3) involved asymmetric photolyses of racemic ethyl α-bromopropionate, $CH_3CH(Br)COOEt$, and *N*,*N*-dimethyl-α-azidopropionamide, $CH_3CH(N_3)CON(CH_3)_2$ (**74**). A few additional reports of successful asymmetric photolyses appeared in the literature (3) between 1930 and 1974, when Kagan and co-workers published their classic paper (207) describing the asymmetric photolysis of camphor. In this study, using GC and polarimetry, they isolated and examined the unphotolyzed camphor remaining after subjecting DL-camphor in hexane to varying extents of photolysis with 313 nm CPL. Using the known value of $g = 0.09$ at 310 nm for camphor, the optical purities of the residues were measured and found to fit closely to the values predicted from their tables (207). At 99% completion of photolysis the residual camphor had an enantiomeric purity of 19.9 ± 2%, by far the highest recorded for any asymmetric photochemical reaction. The authors also extended Kuhn's asymmetric photolysis of **74** to varying extents of completion, finding that the enantiomeric purities of the residues, calculated on the basis of $g = 0.02$, agreed reasonably well with the observed values.

In 1977 Bonner and co-workers (221) undertook a detailed study of the asymmetric photolysis of DL-leucine as a "prebiotically important substrate."

Employing 212.8-nm CPL from a laser source and using analytical GC to estimate the extents of photolysis and the enantiomeric compositions of the unphotolyzed leucine residues, they found that a stereoselective photolysis of D-leucine occurred with RCPL and of L-leucine with LCPL. The enantiomeric excesses produced were 1.98% (L > D) at 59% photolysis with RCPL and 2.50% (D > L) at 75% photolysis with LCPL, these precisely "equal and opposite" enrichments being the second highest ever reported during asymmetric photolyses. No accompanying photoracemization was noted. Implications of the results regarding the origin of optical activity and the recognition of extraterrestrial life were pointed out. In the same year Norden (222) reported the asymmetric photolyses of racemic tartaric acid, alanine, and glutamic acid.

Several additional asymmetric photolyses have been reported more recently. Schneider and co-workers (223) reported that the photolysis of the spiropyrazoline **75** to 63% completion led to an optically active residue whose optical purity was ~ 1.7%. Litman and co-workers (224) found that the asymmetric photolysis of the tropone–Fe(CO)$_3$ complex **76** in hexane



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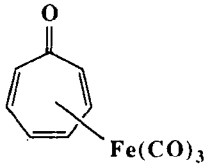


76

with 380–500 nm CPL led, after 3% photolysis, to observed rotations of ~ ±0.01°, depending on the chirality of the CPL employed, thus demonstrating the previously debated fact that **76** could exist in enantiomeric forms. In a somewhat related vein Norden (225) has discussed the possible use of CPL photolysis at low temperatures (77°K) to obtain information on molecules having low inversion barriers at ambient temperatures, but which might be frozen into enantiomeric conformations at low temperatures. Rau and co-workers, and Tran and Fendler (226) have recently discussed closely related subjects involving CPL, and other aspects of the subject have been reviewed on several recent occasions (208, 227).

d. Sources of Circularly Polarized Light. It has long been taken as axiomatic that solar UV radiation was abundantly available and a prime energy source on the primitive Earth, and many experiments have been conducted demonstrating that UV light, acting on plausible "prebiotic" mixtures of gaseous or other molecules, is capable of producing a variety of amino acids, lower aliphatic acids, and other simple organic compounds

(228). For such light to be implicated in the origin of enantiomeric inequalities by any of the photochemical mechanisms discussed above, it must of course have been available on the primitive Earth with a predominant and persistent circular or elliptical polarization. Early authors assumed that this was the case, but only vague suggestions were forthcoming as to the specific mechanism(s) of CPL production (3), and no estimates were given as to the magnitude of any net polarization. These questions are still of paramount interest today.

It is well known (229) that sunlight becomes linearly polarized by reflection from a specular surface or by Rayleigh or Mie scattering from atmospheric molecules or aerosols, and linear polarization has also been documented in submarine environments (230). Linearly polarized light may be changed to CPL by additional reflections (229) or by multiple scattering from aerosols (231), the latter being presumably responsible for the small CPL component in the reflected light from Jupiter, Venus, and Mercury (231,232). Hokkyo (233) has recently suggested that the circularly polarized radio-frequency solar bursts associated with sunspot activity may have been implicated in the origin of optical activity.

Circular polarization in the light from the sky, produced by scattering from aerosols, has recently been measured experimentally. In 1972 Angel et al. (231) detected 0.25% LCPL in the 780–880 nm skylight at the horizon shortly before sunrise, and 0.2% RCPL for such light shortly after sunset. In 1984 Wolstencroft found (234) that the circular polarization of both 582- and 350-nm skylight from a particular direction in the sky went through a minimum between sunrise and noon and then through a maximum between noon and sunset, as shown schematically in Figure 7. While the net circular polarization of light received from the entire sky at any point on the surface of a totally flat "billiard ball" Earth would be zero (234), Wolstencroft points out that a sloping terrain (e.g., a mountain range), which caused partial obscuration of portions of the sky, could lead to a prevailing net circular polarization of skylight in particular local regions of Earth. As suggested in Figure 7,

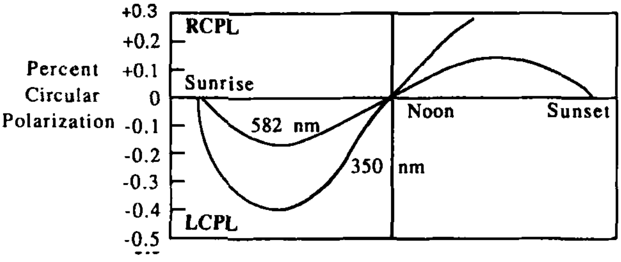


Figure 7. Circular polarization of daylight in a fixed direction. (From Wolstencroft, 234).

any such polarization should cancel on a diurnal basis, and it is furthermore difficult to see how there would be any net preference for CPL chirality when integrated over the entire surface of the globe. However, if the overall asymmetry of Earth's land mass did in fact allow for a prevailing chirality for the CPL received on Earth from skylight, the diurnal CPL variation suggested in Figure 7 would not necessarily result in an overall cancelling effect. The warmer afternoon environments would clearly cause rate increases in subsequent amplification reactions which followed the initial production of small enantiomeric excesses by temperature-independent CPL processes, and preferential enhancement of the chiralities of the CPL products initially formed in the warmer afternoon environments would tend to occur.

In 1971 Mörtberg (235) offered an alternative suggestion for the net chirality sense of terrestrial CPL. Because of the Faraday effect, the RCPL and LCPL components of linearly polarized light coming down through the upper atmosphere in the presence of the Earth's magnetic field develop increasing differences in their refraction as they traverse the increasing refractive index gradient of the atmosphere. Thus one of the CPL components is preferentially refracted toward the surface of Earth and eventually predominates there. Mörtberg then showed that with a tilted axis with respect to the incoming sunlight and with an elliptical orbit about the sun, there would be a persistent net difference in the amounts of RCPL and LCPL reaching the two hemispheres of the Earth, which would not cancel at any geographical position on Earth during its yearly orbit. The oversights in Mörtberg's arguments which potentially invalidate his hypothesis, principally the precession of the equinoxes and geomagnetic reversals, were recently pointed out by Bonner and Rubenstein (236), who then suggested that the hypothesis might nevertheless be salvaged by noting that Earth's land mass has an overall global asymmetry.

The most recent suggestion for the genesis of CPL that might be implicated in originating terrestrial enantiomeric inequalities is that of Bonner and Rubenstein (236, 237) involving circularly polarized synchrotron radiation from the neutron star remnants of supernova explosions. In this scenario UV synchrotron CPL, produced off-angle to the orbit of the electrons circularly accelerating around the rapidly rotating neutron star remnants of supernovae, interacts with the organic mantles of inorganic grains in intergalactic dust clouds, asymmetrically processing the racemic constituents of the organic mantles. As the solar system periodically traverses these interstellar clouds during its 110-million-year journey around the center of our galaxy, vast quantities of organic matter are accreted by Earth—organic matter that already possesses enantiomeric excesses resulting from its stereoselective processing by the synchrotron CPL. The neutron star–synchrotron CPL hypothesis predicts that the chirality sense of biomolecules of extraterrestrial life forms need not be similar to that observed on Earth, but could vary randomly throughout the Universe. Unfortunately, this scenario is not amenable to overall experimental verification, although a number of its individual steps have been observed in the laboratory (236).

While several authors have suggested that formaldehyde polymers, polysaccharides, and other complex organic polymers might constitute the major ingredients of interstellar grains (238), only Khasanov and Gladyshev (239, see also 240) have so far suggested that optically active molecules, formed by unspecified asymmetric force fields, might arise in interstellar dust clouds and persist as a result of the low temperatures and infrequent collisions inherent in such an environment.

7. *Conclusions*

In view of the extensive efforts expended in attempts to validate experimentally the various determinate mechanisms for the origin of enantiomeric excesses, it is somewhat discouraging that so little has been forthcoming in the way of positive results. The Vester–Ulbricht hypothesis, the motivating factor behind so many of these efforts, has yet to be substantiated in any way experimentally, and the direct effects of chiral radiation have been either nonreproducible or uniformly below the threshold of unambiguous observation. Theoretical calculations of the parity violating energy differences between enantiomers have led to values so low that it is hard to entertain seriously the possibility of PVED implication in chiral symmetry breaking. The only parity violation experiments not yet questioned and found wanting are the stereoselective radical formation studies of Akaboshi on alanine enantiomers using the β-radiation from ^{90}Y (99) and ^{3}H (103), his stereoselective recoiled ^{32}S experiments with alanine and serine (108), the stereoselective crystallization experiments in the presence of ^{32}P β-radiation described by Kovacs (129, 130), and the stereoselective γ-radiolyses of phenylalanine enantiomers reported by Merwitz (184). In this slim array of positive results only Akaboshi's ^{90}Y experiments (102) and Merwitz's γ-radiolysis experiments (185) have been independently confirmed in another laboratory. Such considerations, perhaps, led Keszthelyi in 1984 (166) to disavow any aspect of parity violation as a viable mechanism for the origin of optical activity.

While mechanisms based on parity violation have thus proved inconclusive, the potential bright spot in the determinate mechanism picture would appear to involve a mechanism which is also historically the oldest, namely, one based on the action of circularly polarized light. Here we are confronted not with a *theoretical* effect of 1 part in 10^{17} but, in the case of Kagan's asymmetric photolysis of camphor (207), with an experimental effect of 1 part in 5! The effects observable with CPL thus not only can be relatively large, but they are quite reproducible, are strictly reversible on changing the chirality sense of the CPL, and have been obtained in a variety of reaction systems. With the recent experimental demonstrations (231, 234) of the availability of CPL in the daytime sky, it would appear that CPL-mediated reactions, particularly stereoselective photolyses, may provide the most likely determinate mechanisms for the origin of the enantiomeric bias in nature.

It is interesting that a general refutation of physical mechanisms, particularly the action of CPL, for the origin of optically active molecules in nature, has been attempted recently by Gonzalez (271), who argues that the homochiral molecules characteristic of our biosphere cannot logically be accounted for by such mechanisms, that they provide "an extraordinary exception to the second law of thermodynamics," and that they constitute "troublesome gaps in the Theory of Evolution." The many flaws in these "Creationist" criticisms have more recently been pointed out by Brewster (272).

IV. THE AMPLIFICATION OF SMALL ENANTIOMERIC EXCESSES

Except in some of the crystallization experiments and lattice controlled solid-state reactions discussed above (Sect. III-A-2–4), the enantiomeric excesses produced by the chance or determinate mechanisms that we have considered as candidates for the origin of optical activity have proved to be relatively small, ranging from $\sim 20\%$ in asymmetric photolysis to $\sim 10^{-17}$ for the theoretical excesses resulting from PVED effects. Thus authors on these subjects have generally recognized and emphasized the crucial need for subsequent amplification mechanisms which would be capable of promoting such small enantiomeric excesses into the homogeneous chirality sense characteristic of our current biosphere. In view of this commonly recognized need it is therefore surprising that such a relatively small number of experimental investigations have been directed toward the amplification question. In the following sections we summarize the results of these studies.

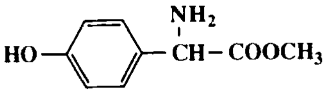
A. Amplification During Evaporation and Precipitation

It has long been known (241, 269) that for many optically active substances, including amino acids, the solubility of the racemate and its individual enantiomeric components are different. In cases where the solubility of the pure enantiomers is greater than that of the racemate, an evaporative process may serve selectively to concentrate in solution that enantiomer which exists in a slightly higher initial concentration. Morowitz (241) developed a simple mathematical model for this system and tested its predictions experimentally by taking saturated solutions of DL-phenylalanine and DL-isoleucine, adding varying small quantities of each corresponding L enantiomer, allowing equilibration, evaporation, and partial precipitation to occur, removing the precipitate, and examining the supernatants polarimetrically. The observed enantiomeric excesses in the supernatants increased quite exactly, as predicted by his mathematical model, demonstrating that very small asymmetries may be appreciably amplified by a simple process such as evaporation.

Several years later Wagener (182) examined various physical processes whose effects, because of PVEDs, would be expected to differ slightly between enantiomers. Such processes included chromatography, ion exchange, electrophoresis, polymerization, and precipitation, and each was considered from the viewpoint of its possible efficacy in amplifying the small enantiomeric excesses predicted as arising from the PVEDs. After analyzing the difficulties inherent in each type of experiment, Wagener concluded that precipitation experiments had the greatest likelihood of success. In the same year Thiemann (242), extending his earlier precipitation experiments (180) and extending Wagener's conclusions (182), pointed out that if a racemate is more soluble than either of its enantiomeric components, there will be an enrichment of the predominant enantiomer during precipitation from a saturated solution of nonracemic composition. He then attempted to use this phenomenon to test for small "asymmetry effects" in the precipitations of racemic asparagine samples. Very small but definite enrichments, as measured polarimetrically at 250 nm, were found in the precipitates, with D > L in precipitations conducted at < 7.5°C and L > D in those conducted at > 8°C. Unfortunately, no attempts were made to utilize the technique for the amplification of enantiomeric excesses larger than those arising spontaneously in the DL-asparagine.

B. Amplification During Incomplete Reaction

The stereoselective course of the incomplete reaction between two optically impure substances was first analyzed theoretically and experimentally by Langenbeck and Triem in 1936 (3). They found that if tyrosine methyl ester (**77**) having an L > D enantiomeric excess of 27.4% was converted thermally to the dimer **78**, and if the reaction was interrupted at 40% completion, the dimer product contained tyrosine residues in which the L > D excess had increased to 30.8%. Thus a 3.4% enhancement in the optical purity (enantiomeric excess) of optically impure **77** attended its partial conversion to **78**. Analogous diastereomeric selectivities leading to enantiomer enhancements on incomplete reactions of optical isomers have also been reported more recently.



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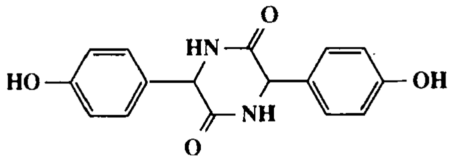

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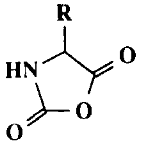

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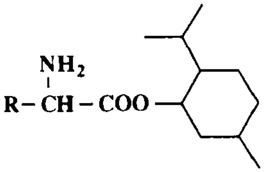
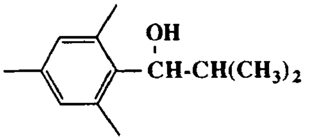


80

Hayakawa and co-workers (243) investigated the reactivities of the *N*-carboxyanhydrides of DL-alanine, -valine, and -phenylalanine (**79**, R = Me, *i*-Pr, and $PhCH_2$, respectively) with a 50% deficiency of (−)-menthol, to form the diastereomeric (−)-menthyl esters (**80**). The esterification rates for the D amino acids were found to be higher than those of the L in all cases, leaving the unreacted amino acid derivative **79** always enriched in the L form. In 1973 Horeau reported (244) that when 10 equivalents of mesitylisopropylcarbinol (**81**) having an enantiomeric excess of 20% reacted completely with 9 equivalents of α-phenylbutyryl chloride (**82**), the 1 equivalent of unreacted carbinol **81** remaining now had a 50% enantiomeric excess, thus showing that the optical purity of an enantiomerically enriched reactant could be increased on its partial reaction with a molar deficiency of a racemate. He demonstrated this (245) in another context shortly thereafter, reporting that when an excess of racemic α-phenylbutyric anhydride (**83**) reacts with a deficiency of (+)-α-phenylethanol (**84**), the (−)-enantiomer of **83** reacts faster, producing an ester product enriched in the diastereomer resulting from (−)-**83** and (+)-**84** and



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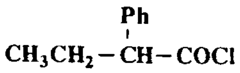
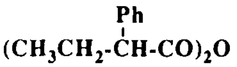


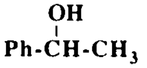
$CH_3CH_2-\overset{Ph}{CH}-COCl$

82



$(CH_3CH_2\text{-}\overset{Ph}{CH}\text{-}CO)_2O$

83



$Ph\text{-}\overset{OH}{CH}\text{-}CH_3$

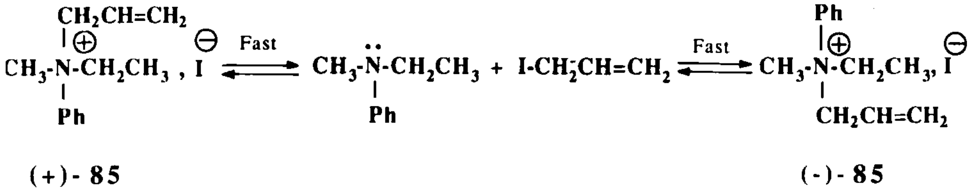
84

leaving (+)-**83** in excess in the unreacted residue. Horeau then developed a formula for calculating the percentage of a mixture of enantiomers of one optical purity that would have to be consumed in such a process to have its optical purity enhanced to an arbitrary higher value (e.g., 99.9%), and demonstrated the application of the formula experimentally. Finally, Briaucourt and Horeau showed (246) that if optically impure (+)-**82** acts on optically impure (−)-**81** in an incomplete reaction, the unconsumed reactants have higher optical purities than they had at the outset. They then showed that by a successive series of such partial esterification steps the optical purities of the residual reactants could each be amplified to ~100%, demonstrating again the efficacy of incomplete diastereomeric reactions between optically impure reactants to amplify small enantiomeric excesses.

C. Amplification During Stereoselective Autocatalysis

Mathematical and pictorial models for spontaneous symmetry breaking (Sect. III-A-1), of which Calvin's "stereospecific autocatalysis" mechanism (Figure 1) is a simple prototype, involve critical "feedback" steps which, of course, permit small enantiomeric excesses to become amplified. While originally proposed to amplify the results of "statistical fluctuations" in chance mechanisms, such schemes can also be applied with equal validity to the amplification of small enantiomeric excesses generated by determinate mechanisms, and indeed they have been widely called upon to do so in connection with the amplification of minute excesses arising from PVED effects. In view of this, it is perhaps surprising that so little effort has been expended to validate such models experimentally.

The first experimental demonstration of such autocatalytic amplification was that of Havinga in 1941 (3), who showed that *N*-methyl-*N*-ethyl-*N*-allylanilinium iodide (**85**), whose enantiomers are in mobile equilibrium via the dissociation depicted in Scheme 3, undergoes spontaneous resolution on crystallization from supersaturated chloroform solutions. Here the initially (randomly) formed slight excess of one antipode of **85** acts as a seed to amplify its own growth, since the equilibrium of the **85** enantiomers shifts rapidly to



$$\underset{\text{Ph}}{\overset{\text{CH}_2\text{CH=CH}_2}{\text{CH}_3\text{-}\overset{\oplus}{\text{N}}\text{-CH}_2\text{CH}_3}}\text{, }\overset{\ominus}{\text{I}} \xrightleftharpoons{\text{Fast}} \underset{\text{Ph}}{\text{CH}_3\text{-}\overset{\cdot\cdot}{\text{N}}\text{-CH}_2\text{CH}_3} + \text{I-CH}_2\text{CH=CH}_2 \xrightleftharpoons{\text{Fast}} \underset{\text{CH}_2\text{CH=CH}_2}{\overset{\text{Ph}}{\text{CH}_3\text{-}\overset{\oplus}{\text{N}}\text{-CH}_2\text{CH}_3}}\text{, }\overset{\ominus}{\text{I}}$$

(+)-85 (-)-85

Scheme 3

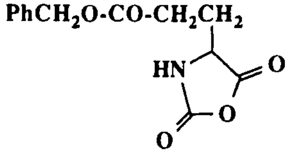
compensate for the removal of the enantiomer in initial excess as it crystallizes from solution. The previously discussed stereoselective formation of one particular enantiomer during crystallizations of racemic 1,1′-binaphthyl (Figure 2) has also been offered (34, 35) as an additional example of the autocatalysis mechanism of Figure 1.

Experimental attempts to demonstrate autocatalytic amplification in a different context have been undertaken recently by Addadi and co-workers (50), who attempted to use their photodimerization and polymerization reactions (Figure 4) in an autocatalysis scheme which they hoped would provide a model for the origin of chirality. They designed a system to test whether a chiral polymeric product of such a reaction might, in a "feedback" step, induce a preferred crystallization of its parent monomer, which would in turn subsequently polymerize into additional polymer of the same chirality. Referring to Figure 4, in a typical experiment the optical active dimer from racemic **12** [X = (±)-*s*-Bu] was used as "seed" to influence the crystallization of achiral **12** [X = 3-pentyl], and the crystals of the latter were irradiated to produce its corresponding dimers and polymers. If the (+)-dimer from racemic **12** [X = (±)-*s*-Bu] was used as "seed," the resulting crystals of monomer consistently afforded (−)-polymeric products (**13**), and vice versa. This "inversion effect" was explained by assuming that the (+)-dimer seed acted as a "stereochemically similar impurity" to inhibit crystal growth of that monomer which originally produced it. The inversion effect was shown to be a general phenomenon in crystal growth, wherein the selective incorporation of tiny amounts of impurities on the growing sites of a specific crystal face dramatically inhibits the relative growth of this face with respect to the rates of growth of the other faces of the same crystal. The inversion effect thus constituted a fatal "negative feedback" in the proposed autocatalysis scheme and, after studying a wide variety of related photopolymerization systems from this viewpoint, the authors concluded that the solution of the amplification problem, that is, the elimination of the inversion effect, "will thus require very specially designed experiments" (50).

The potential importance of autocatalytic feedback steps to amplify small enantiomeric excesses resulting from processes involving weak neutral current effects has again been emphasized recently by Kondepudi and Nelson (247), who have proposed a chemical system in which such an amplification might occur. The system involves a rhodium hydrogenation catalyst (in which "weak-neutral-current energies should be high") having chiral ligands which can not only bring about stereoselective hydrogenation but also have the ability to breed catalytically additional ligands of similar chirality sense from an appropriate achiral substrate. In such a system, beginning with a metal catalyst and an achiral substrate, "the catalyst can breed its own chirality and a chiral product will be autocatalytically produced." The details of such an experiment were not suggested, however, and needless to say the experiment has yet to be performed. Nor was it made clear, for that matter, how catalytic hydrogenation might be relevant to the environment of the prebiotic Earth.

D. Amplification During Polymerization

In 1957 Wald (11), arguing that "optical activity appeared as a consequence of intrinsic structural demands of key molecules of which organisms were eventually composed," suggested that adoption of the chiral α-helix coil in the secondary structure of proteins permitted them to select one amino acid enantiomer in preference to its antipode during their growth. In this scenario, as the polypeptide chain grew it preferentially selected amino acid monomers having a configuration identical to those already existing in its α-helix. These conclusions followed from the assumptions that the most stable α-helix would result from a homochiral sequence of amino acids, and that a sequence having a random distribution of configurations in the protein chain would make an extended α-helix impossible. Experiments by others at the same time seemed to substantiate Wald's suggestion. Thus, in a series of studies (3) involving the base-initiated polymerization of γ-benzyl glutamate *N*-carboxyanhydride (γ-benzyl glutamate NCA, **86**) to poly(γ-benzyl glutamate), **87**, it



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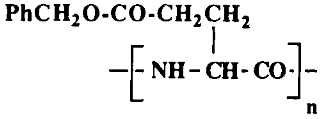
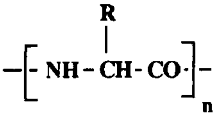


$$-\!\left[\mathrm{NH-\overset{\overset{\displaystyle PhCH_2O\text{-}CO\text{-}CH_2CH_2}{|}}{CH}-CO\text{-}}\right]_n\!-$$

87



$$-\!\left[\mathrm{NH-\overset{\overset{\displaystyle R}{|}}{CH}-CO\text{-}}\right]_n\!-$$

88

was found that the α-helix of L-**87** was progressively weakened as D units replaced L units in its chain, that the rate of polymerization of DL-**86** was only 5% that of L-**86**, that the rate of polymerization of L-**86** was slow up to about an $n=8$ oligomer (where the α-helix becomes viable), after which an abrupt five- to sixfold rate increase occurred, that the introduction of as little as 5%

L-**86** to 95% D-**86** reduced the polymerization rate to only one-third the value observed for optically pure D-**86**, and that the degree of polymerization achieved by DL-**86** was only ~20% that achieved by the optically pure forms of **86**. These as well as other closely related experiments performed in the late 1950s (3) were thus all in accord with Wald's suggestion of an α-helix mediated stereoselection of amino acids of one configuration during their polymerization to polypeptide chains.

The first direct experimental demonstration that amplification of enantiomeric excess did in fact accompany these stereoselective polymerizations was that of Matsuura and co-workers in 1965 (248), who polymerized a mixture of D- and L-alanine NCAs (**79**, R = Me) having the L monomer in excess. The polyalanine products (**88**, R = Me) were isolated at various stages of completion of the reaction and their specific rotations in trifluoroacetic acid solution were measured polarimetrically. The rotations decreased to a minimum at ~50% completion, then increased to the starting value at 100% completion, indicating that the initially predominant L-alanine NCA was being preferentially incorporated in the early stages of the polymerization, and the D-alanine NCA only in the latter stages. The stereoselective amplification was attributed to both the configuration of the terminal group in the growing polymer chain, and particularly to its α-helical structure. These results were confirmed and extended by Tsuruta and co-workers (249) two years later. They measured the rotations of the polymers as a function of the enantiomeric excess of the L-alanine in the starting monomer **79** (R = Me), and found that the polymer rotation was lower the greater the excess of L-**79** (R = Me) in the monomer. Inoue and co-workers (250) made similar findings using L > D mixtures of γ-benzyl glutamate NCA monomers (**86**). In contrast Akaike and co-workers (251), polymerizing various L > D mixtures of valine NCA monomers (**79**, R = *i*-Pr), noted that while the degree of polymerization showed the usual increase with percent completion of the reaction, there was no concomitant stereoselective incorporation of the L monomer into the polymer. In these cases the optical rotations were constant for particular starting D/L monomer ratios regardless of the extent of reaction, indicating a constant content of L valine in the polymer chains throughout the polymerization. The lack of stereoselection in valine NCA polymerizations resulted (251) because the growing valine polymer was not able to form an α helix owing to steric hindrance, but rather adopted the secondary structure of a β-sheet conformation.

The interpretation of such observations is complicated, however, by the multifarious experimental parameters that affect the outcome of such polymerizations. Such parameters include the solvent in which the polymerization is conducted, the nature of the base initiating the polymerization, the initiator/substrate ratio, and the structure of the amino acid in the NCA monomer. To illustrate briefly, isoleucine NCA (**79**, R = *s*-Bu) does not polymerize stereoselectively when certain secondary amines act as the initiator, but both isoleucine and valine NCAs showed stereoselective polymerizations when tertiary amines such as Bu_3N were the initiators (252). Because of the varying results obtained as a consequence of such parameters, NCA polymerizations have been studied in great variety and detail from a mechanistic viewpoint in recent years, particularly in Japan (253). Not only the α-helix itself, but also the chirality sense of the end and penultimate units in the growing polymer chain, as well the intimate details of the possible polymerization mechanisms appear to be implicated in the presence or absence, and the degree of stereoselectivity, observed during NCA polymerizations. It is quite beyond our scope to consider the details of these studies, however, and the interested reader is referred to the original literature (253).

Extending the earlier experiments of Matsuura (248) and Tsuruta (249), where conclusions were based on polarimetric observations of the starting monomer NCAs and the polymer products, Blair and Bonner (254) in 1980 undertook a quantitative investigation of the amplification occurring during the polymerization of the NCAs of leucine (**79**, R = *i*-Bu) and valine (**79**, R = *i*-Pr), using GC, however, as the analytical criterion. The general procedure was to induce partial polymerization in mixtures of D- and L-leucine NCAs, for example, containing known excesses of either the D- or L-enantiomer, then to analyze by GC the enantiomeric compositions of the resulting polymers (after hydrolysis) to see quantitatively how much the original enantiomeric excess (e.e.) of each starting NCA monomer might have been enhanced. The unpolymerized residual NCA monomers were also hydrolyzed and the enantiomeric compositions similarly determined by GC as a check for internal consistency, since any e.e. increase observed in the polymers should be balanced by a corresponding e.e. decrease in the unreacted monomers. As a further symmetry check, replicate polymerizations were conducted using both D- and L-enantiomers in approximately equal initial excess in the NCA monomers, to see if the predicted "equal and opposite" e.e. changes could be observed.

In this study, summarized briefly in Table 3, it was found that polymerizations to the extent of ~50% of leucine NCA monomers containing increasing e.e.'s of either enantiomer resulted uniformly in polymers showing an e.e. enhancement of that enantiomer initially in excess in the monomer. Also, as predicted for polymerizations going to 50% completion, the residual unreacted leucine NCA monomers showed an approximately equal *decrease* in the e.e. of the originally predominant enantiomer. Enhancement of the e.e. of the predominant monomer was also found to be greater as the initial e.e. in the monomer increased until a plateau value was reached, after which the e.e. increase found in the polymer appeared independent of the e.e. of the starting

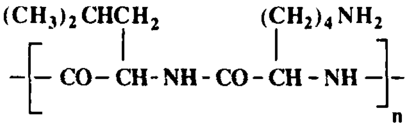
Table 3
Partial Polymerization of Leucine NCAs of Increasing Enantiomeric Excesses

Initial Leu NCA		Completion of Polymerization	Hydrolyzed Product			
			Polymer		Unreacted NCA	
Excess of	e.e.[a] (%)	(%)	e.e.[a] (%)	Δ[b] (%)	e.e.[a] (%)	Δ[b] (%)
D	8.5	51	11.8	3.3	5.1	−3.4
D	8.7	53	12.3	3.6	4.5	−4.2
L	9.0	54	13.3	4.3	4.7	−4.3
L	27.0	56	39.5	12.5	18.3	−8.7
D	31.2	52	42.1	10.9	21.8	−9.4
L	50.6	54	57.9	7.3	42.1	−8.5
L	69.6	53	77.0	7.4	61.1	−8.5

[a] Absolute value of %D−%L.
[b] Product e.e.–initial e.e.

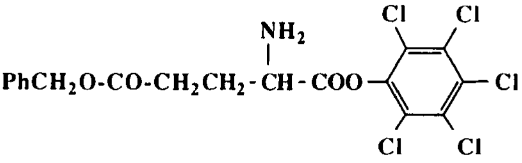
monomers. Quite the reverse effects were noted, however, in partial polymerizations of valine NCA monomers. Here it was found that the e.e. of the initially predominant enantiomer was *lower* in the polymer and *higher* in the unreacted monomer, and that the e.e. changes in each were independent of the extent of reaction over the range studied. These results were interpreted as indicating that the racemate of the valine NCA monomer was being preferentially incorporated into the polymer, and were exactly the opposite to what would occur by the α-helix mediated stereoselection of a single enantiomer, as originally proposed by Wald. The data were in accord, however, with the earlier observations of Akaike (251) that the polyvalines from a given enantiomeric ratio of valine NCA monomers had a constant ratio of enantiomers in the chain, regardless of the extent of polymerization. Clearly, Wald's α-helix selection hypothesis would appear to be applicable only to those peptides adopting an α-helical secondary structure, and not, as suggested by Akaike (251), to those constrained to a nonhelical β-sheet secondary structure.

That β-sheet structures, which can also exist as chiral entities, may likewise be implicated in amplifying enantiomeric excesses during the formation of polypeptides has been recently argued, however, by Brack and Spach in France (255), who have attempted to compare α-helices and β-sheets from this viewpoint. Their experiments started with the synthesis of a series of 5 poly(leucyl–lysyl) peptides (**89**) having alternating hydrophobic (leucyl) and hydrophilic (lysyl) residues whose configurations were randomly distributed



$$-\left[-CO-\overset{(CH_3)_2CHCH_2}{\overset{|}{CH}}-NH-CO-\overset{(CH_2)_4NH_2}{\overset{|}{CH}}-NH-\right]_n-$$

89



90

along the peptide chains, but evenly shared among the leucyl and lysyl residues. The polymers were prepared by condensations of activated L-Leu-L-Lys, L-Leu-D-Lys, D-Leu-L-Lys, and D-Leu-D-Lys dipeptides in particular proportions, such that the total D/L ratios in the polymers could be controlled. The polymers were then dissolved in D_2O containing $NaClO_4$ to varying ionic strengths, whereupon β-sheet conformations were believed to form. The IR spectra and circular dichroism of such solutions were then measured and from them, by a series of assumptions and complex calculations, the overall β-sheet fraction as well as the fractions of L and D residues in the β-sheets were estimated for each polymer. From such measurements and calculations it was concluded that the formation of β-sheet structures in such polymers with alternating hydrophobic–hydrophilic monomer components became complete in aqueous solution as the ionic strength was increased, and if monomer residues of opposite configurations were progressively introduced into the polymer chains, the formation of β structures was progressively depressed. The calculations also showed that the β-sheet structures became rapidly enriched in L-residues when the ratio of L/(L + D) residues in the polymer increased from 0.5 to 1.0, and that with ratios of 0.75 or higher the polymer consisted of essentially optically pure β-sheet cores having configurationally similar amino acid constituents attached to random-coil portions containing both D- and L-residues. Thus if the stereocomposition of the polymer components is nonracemic, the polymer could be described as formed of β-sheet nuclei highly enriched in one enantiomer, with the rest of the chains in a disordered state (Figure 8). Such polymers were finally subjected to gentle hydrolysis (256) when it was observed that the hydrolysis rates were characterized by two pseudo-first-order rate constants, which would be characteristic of two conformational components in the polymers. The random-coil portions of the polymers were apparently hydrolyzing more rapidly, which allowed the isolation of unhydrolyzed β-sheet fractions enriched in one

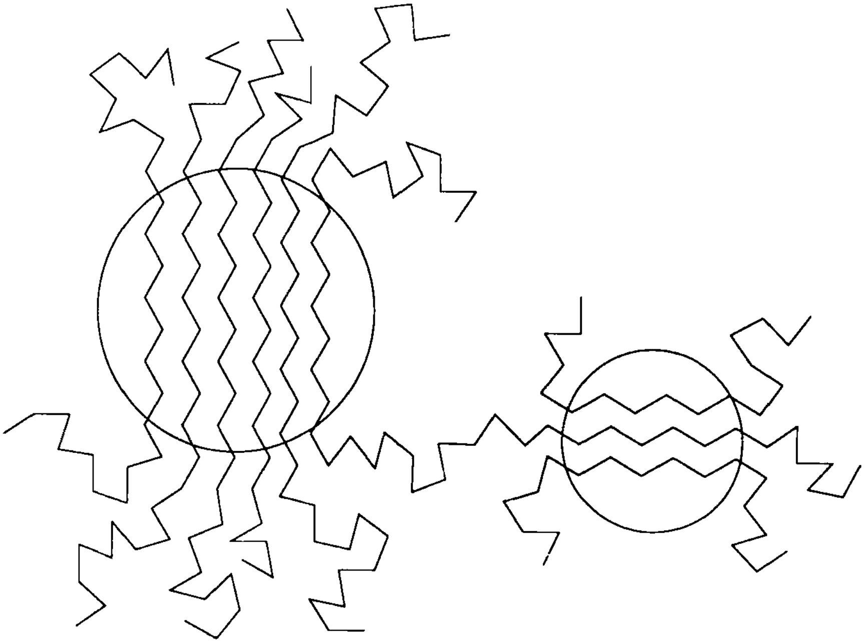


Figure 8. Poly-(D ≠ L)-peptide chain with β-sheet nuclei (circled) surrounded by random-coil chains.

enantiomer. The authors emphasized that such a process would be plausible for the enrichment of an initially predominant enantiomer during prebiotic polymerizations.

In earlier related studies Spach (257) investigated the question of whether the helical sense of the α-helix or the configuration of the *N*-terminal amino acid residue in the growing chain was the predominant factor in determining the course of polymerization. The procedure in these experiments was to start with preformed γ-benzyl glutamate polymers (**87**) having a preexisting helical chirality but having *N*-terminal propagating groups of either the D or L configuration. These preexisting **87** polymers were then used to initiate further polymerizations with monomers consisting of D or L enantiomers of the pentachlorophenyl esters of α-benzyl glutamate (**90**). By studying the initial rates of these further polymerizations, qualitative conclusions could be made regarding the relative importance of the chirality sense of the α-helix versus the configuration of the *N*-terminal propagating group. The following preformed polymers of **87** were employed: (a) $(\text{LD})_n$; (b) $(\text{DL})_n$; (c) D-$(\text{LD})_n$; (d) L-$(\text{LD})_n$; (e) $(\text{LLD})_n$; and (f) $(\text{DLL})_n$. With the **87**-(a) polymer, L-**90** showed the faster rate of further polymerization, with **87**-(b) D-**90** polymerized faster, while in all the other cases the preformed **87** polymers initiated further polymerization of the L-**90** monomer more rapidly, regardless of the chirality of the *N*-terminal propagating end of the initial polymer **87**. From these results it was concluded that the helical conformation of the polymer was more important in determining the rate of polymerization than was the configuration of the *N*-terminal propagating end of the polymer. In a final overall summary of their experiments, Brack and Spach (258) concluded that, while enantiomer enrichment can thus occur during the polymerization of mixtures of amino acid monomers having an excess of one enantiomer via either the α-helix or β-sheet secondary conformations, amplification via β-structures should be more probable on the prebiotic Earth since, as they categorically stated, "short peptides preferentially adopt a β-conformation which is in turn more stable in solution than the α-helix." Experimental evidence supporting this statement was not cited.

In 1974 Thiemann and Darge (259) investigated the possibility of using NCA polymerizations as a means of detecting intrinsic rate differences in the reactions of D and L enantiomers, which might be amplified during the polymerization process. They conducted the polymerizations of the NCA derivatives of carefully racemized samples of alanine, α-aminobutyric acid (ABA), and ε-carbobenzoxylysine [**79**, R = Me, Et, $PhCH_2OCONH(CH_2)_4$, respectively], then measured the optical rotations at 310 nm of the polymer products (as well as that of a 1:1 Ala–ABA copolymer) in trifluoroacetic acid. Taking particular pains to avoid experimental artifacts, they observed uniformly negative rotations in all of the six polymers prepared, rotations ranging from $-0.00025°$ to $-0.00084°$ ($\pm \sim 0.00025°$). This suggested to them that there was an intrinsic difference in the polymerization rates for L- and D-amino acid NCAs of $\sim 8 \times 10^{-6}$, a difference they attributed to the stereoselective effect of an (unspecified) physical force. Unfortunately, no one has yet attempted to duplicate these interesting observations in the laboratory. In this connection, however, Yamagata and co-workers (260) carried out a number of "computer experiments" simulating prebiotic polymerizations. Assuming small initial asymmetries in the chemical properties of the original enantiomeric monomers (due to PVEDs), they found that a high degree of selection of one enantiomer was evident in some of their polymerization models. While the asymmetry in the polymers increased with the degree of polymerization, it developed much more slowly than the growth of the polymers, and was not evident at all in cases where the growing polymer was not simultaneously exposed to the competing effects of possible hydrolysis (i.e., in nonaqueous systems) or some other polymer degrading process.

The potential importance of hydrolysis in an overall mechanism for the amplification of enantiomeric excesses in amino acids during α-helix mediated polymerizations was first shown experimentally by Bonner and co-workers in 1981. These investigators (261) subjected a number of polymers of D-, L-, and DL-leucine (**88**, R = *i*-Bu) having similar chain lengths to partial hydrolysis under comparable conditions, and found that the extents of hydrolysis undergone by the poly-DL-leucine samples were considerably greater than those for the poly-D-leucine or poly-L-leucine samples, indicating a greater stability toward hydrolysis for the homochiral polymers. Extending these observations, they also reported experiments on the partial hydrolysis of an enantiomerically impure polyleucine sample, in which analytical GC was used as the criterion for enantiomeric excesses. When a leucine polymer having an L > D e.e. of 45.4% was subjected to partial hydrolysis to the extents of 10.4, 16.9, and 27.0%, for example, the residual unhydrolyzed polymers were found to have e.e.'s of 49.5, 50.1, and 54.9%, respectively, indicating enantiomeric enrichments (e.e. enhancements) of 4.1, 4.7, and 9.5%, respectively, as a result of the partial hydrolyses. Corresponding decreases in the e.e.'s of the recovered leucine monomers from the hydrolysates were also noted in each case. Clearly, the more optically enriched peptide components of the leucine polymers were more stable to hydrolytic degradation than were the components of lower enantiomeric purity. This conclusion suggested an additional possibility for amplification.

The L > D 45.4% e.e. leucine employed in these experiments had been prepared originally from a mixture of leucine NCA monomers (**79**, R = *i*-Bu) having an L > D e.e. of 31.1%. This represented an e.e. enhancement of 14.3% during the polymerization. As seen above, partial hydrolysis of this polymer to the extent of 27% resulted in a residual polymer having an L > D e.e. of 54.9%. In the combined partial polymerization–partial hydrolysis sequence, therefore, the original e.e. of 31.1% in the starting leucine NCA monomer was increased to 54.9% in the final polymer, representing a total L > D e.e. enrichment of ~24%. Thus a partial polymerization–partial hydrolysis process appeared potentially to be a highly efficient amplification mechanism for small enantiomeric excesses, and it was suggested that such a mechanism, driven by environmental dry–wet cycles, might have been operative to enhance small, abiotically produced enantiomeric inequalities during the polymerization of prebiotic amino acid monomers. In later papers (262) a more detailed model was proposed whereby small e.e.'s produced by indigenous abiotic chiral agents could lead to enantiomerically homogeneous polypeptides in an α-helix mediated partial polymerization and partial hydrolysis sequence having a cyclic "feedback" loop. This is illustrated in Figure 9, where we see that the partial hydrolysis of an initial enantiomerically enriched polypeptide (III) affords a polypeptide (IV) of higher e.e. Polymer IV then initiates further polymerization, stereoselectively incorporating its predominant enantiomer from the pools of monomers (I and II), thus "autocatalytically" producing a polypeptide (V) of even higher e.e. Repetition of this

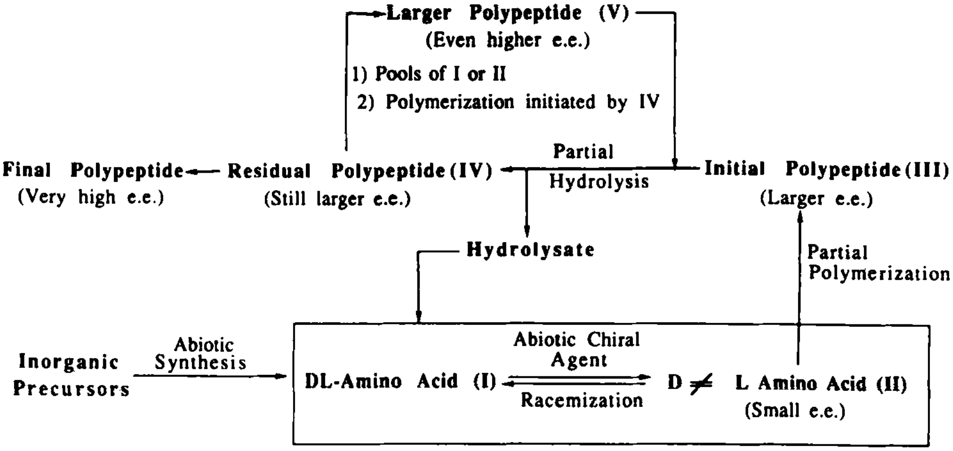

Larger Polypeptide (V)
(Even higher e.e.)
1) Pools of I or II
2) Polymerization initiated by IV
Partial
Hydrolysis
Final Polypeptide
(Very high e.e.)
Residual Polypeptide (IV)
(Still larger e.e.)
Initial Polypeptide (III)
(Larger e.e.)
Hydrolysate
Partial
Polymerization
Inorganic
Precursors
Abiotic
Synthesis
Abiotic Chiral
Agent
DL-Amino Acid (I)
Racemization
D ⇄ L Amino Acid (II)
(Small e.e.)

Figure 9. Model mechanism for the abiotic genesis of homochiral polypeptides.

partial hydrolysis–partial polymerization sequence, contributing to and drawing from the open reservoirs (I and II) of amino acid monomers, would clearly continue to enhance the optical purity of any polypeptides involved in the cyclic sequence. It was pointed out further that the more extensive α-helical structures of the polymers having higher e.e.'s would tend to protect them from racemizing influences that would interconvert the monomers. It was emphasized again that a sequential cyclic process such as that illustrated in Figure 9 could be driven by environmental wet–dry cycles on the primitive Earth, in much the manner proposed by Lahav and co-workers (263) for the thermal oligomerization of amino acids in "fluctuating clay environments," and by Usher (264) for the preferential prebiotic formation of oligonucleotides containing natural 3′,5′-linkages. Joyce and co-workers (16) recently suggested that an analogous autocatalytic mechanism in the replication of polynucleotides might similarly serve as a means for the amplification of enantiomeric excesses.

Early polymerization experiments with γ-benzyl L-glutamate NCA (L-**86**) suggested that the α-helix secondary structure in a polypeptide first became viable at about the octamer stage of polymerization (i.e., L-**87**, $n = 8$), after which the growing α-helix did its own homochiral stereoselection (3). A legitimate question thus arises as to how the original homochiral octapeptide might have formed, prior to the takeover by helix stereoselection. This question has received scant attention. Cloud (265) recently dismissed it with the statement that "chirality may not be as much of a problem as once supposed" since "to get five amino acids or sugars of the same handedness lined up by chance is entirely probable." The chances for the formation of a stereoregular pentapeptide, of course, are 1 in 32, and for an octapeptide 1 in 256. While these may not be insurmountable odds, it should nevertheless be emphasized that for every homochiral L-octapeptide formed by chance, there is an equal probability for the formation of its all-D enantiomer. Cloud's arguments thus leave us confronted with all of the dilemmas inherent in chance mechanisms (Sect. III-A-8).

Goldberg and co-workers (266) recently attempted to address this issue experimentally by observing the inherent stereoselectives as small peptides were built up to larger ones step by step. Two equivalents of a DL-amino acid NCA (DL-AA) were reacted with 1 equivalent of an optically pure L′-amino acid, for example, and the diastereomeric composition of the D-L′ and L-L′ dipeptide product mixture was established. Then 2 equivalents of DL-AA were reacted with 1 equivalent of optically pure dipeptide, to form two tripeptides (e.g., D-L′L′ and L-L′L′). The same was done with optically pure tripeptides to form two tetrapeptides (e.g., D-L′L′L′ and L-L′L′L′). In each case the diastereomeric peptides were formed in unequal amounts, and the percents of major and minor peptide products were determined after each step. Each such competitive process used to form 34 different di-, tri-, and tetrapeptides from alanine, aspartic acid, and glycine, was found to be stereoselective. The majority (70%) displayed biases in favor of isotactic growth (i.e., homochirality), with diastereomeric enrichments ranging between 4.2 and 56.6%. The authors concluded that "isotactic growth of prevital polymers is likely to be an important part of any mechanism that satisfactorily accounts for the enantioselective passage of biomolecules from their racemic beginnings to the stereochemical homogeneity of contemporary life."

The numerous experiments described above attempting to assess the possibilities of enantiomeric enrichment during polymerization have been conducted, of course, with monomer precursors that can hardly qualify as prebiotically probable. Nevertheless, many conclusions have been reached and principles established in these studies which should be applicable to prebiotically realistic circumstances. In this connection, Rohlfing and Fouche (267) have surveyed the extent of racemization of a number of individual L amino acids during their thermal copolymerization with L-glutamic acid and with L-lysine. Several of the amino acids were found not to be extensively racemized during such copolymerizations under hypohydrous conditions at 170–190°C, in contrast to earlier conclusions. In no cases, however, were optically pure amino acids found in the resulting "protenoid" copolymers. The authors have suggested that such stereo-enriched primitive proteinoids might not only be catalytically active in promoting asymmetric syntheses, but also be able to "select" between D and L substrates during such reactions. Such intriguing possibilities, however, remain to be demonstrated experimentally (278).

E. Conclusions

In Sections IV-A–IV-D we have summarized the experimental evidence behind the various suggested mechanisms by which enantiomeric excesses existing in optically impure precursors might be enhanced to yield products of greater optical purity. These processes for amplifying enantiomeric excesses have not been uniformly successful in the laboratory, nor do they appear equally likely in the context of the probable environment of the prebiotic Earth. Amplification during evaporation, precipitation, or crystallization has been observed in only a limited number of rather carefully contrived laboratory situations, and the broader generality of these processes must certainly be demonstrated before their potential prebiotic efficacy can be championed. The same can be said for the few successful crystallization experiments embracing "stereoselective autocatalysis." The amplification of enantiomeric purity during the incomplete reaction of two optically impure reactants can apparently in principle be substantial, but it must always be remembered that enantiomeric enrichment in the products of such incomplete reactions is always accompanied by an enantiomeric depletion in the residual, unused reactants. Thus in a prebiotic setting the particular enantiomerically enriched products formed, rather than the enantiomerically depleted residual reactants, would have to be the sole contenders for further chemical evolution. Thus the viability of all of the amplification mechanisms described above in a harsh prebiotic environment remains conjectural.

In the "amplification during polymerization" mechanism for abiotic amplification of enantiomeric purity, on the other hand, the relevancy to the prebiotic environment is immediately apparent from the obvious fact that today's crucial chiral biomolecules—proteins, DNA, RNA, and polysaccharides—are all polymeric. While the successful model experiments supporting this mechanism may not have been completely realistic from a prebiotic viewpoint, it is nevertheless gratifying and significant that the abiotic amplification of enantiomeric excesses has been demonstrated experimentally in ways that implicate both of the secondary structures of proteins, α-helices and β-sheets. If both of these secondary structures can act stereoselectively during abiotic polymerization reactions to amplify the small enantiomeric excesses which might have arisen among amino acid monomers by any of the "determinate mechanisms" (or "chance mechanisms") for the abiotic origin of enantiomeric inequalities, and if in addition these secondary structures can, as has been shown, act to protect the stereochemical integrity of the polymers formed, the stage is then clearly set for the inevitable development of the current homochirality of our biosphere during the subsequent emergence and evolution of primitive life forms.

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Stereochemical Aspects of Radical Pair Reactions

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I. INTRODUCTION

The past 40 years have brought tremendous understanding to the field of free radical chemistry. From the initial experiments of Gomberg (1) and Paneth (2), which demonstrated the existence of persistent and transient radical species, the growth in understanding the importance of radical species as reaction intermediates has been steady and impressive.

The first burst in research activity involving free radicals came with the onset of World War II. Radical polymerization processes were crucial in the production of plastics and synthetic rubber. Another radical reaction studied extensively during this period was autoxidation, the chain reaction of organic compounds and molecular oxygen. The 1970s and 1980s brought renewed interest because of the suggestion that such radical reactions occur in living systems (3). It should also be noted that in the 1980s free radical chemistry is being used extensively in organic synthesis (4). Free radicals are "the reactive intermediates of the decade" in organic synthetic methodology.

Free radical polymerization, autoxidation, and most of the free radical synthetic processes currently popular, are chain processes made up of reactions in which the site of the unpaired electron changes position. Pairs of radicals are generally important in the initiation and termination of such chain reactions, however. Pairs of free radicals are also implicated in biological processes, such as the initiation of peroxidation and other oxygenation processes. Cytochrome P-450, for example, is an enzyme that catalyzes the reaction shown in eq. [1] and the mechanism written (5) for these conversions is suggested to involve an alkyl radical–metal oxo species pair, **1**. The stereochemistry of P-450 catalyzed oxygen insertion has provided important evidence concerning the mechanism of this conversion and the nature of pairs of radicals in biological systems that involve molecular aggregates (substrate–enzyme complexes) and hydrophilic–hydrophobic interfaces is thus of some interest.

$$\mathrm{R\text{-}H + O_2 \xrightarrow[H_2]{P\text{-}450} R\text{-}OH + H_2O} \qquad [1]$$

$$\textit{via} \qquad \underset{\mathbf{1}}{[\mathrm{R\bullet + H\text{-}O\text{-}M}]}$$

This chapter is an outgrowth of our longstanding interest in free radicals and pairs of free radicals. Any discussion of pairs of free radicals requires a rudimentary knowledge of free radical structure and terminology and we present a brief background on this topic. We then turn to the nature of radical pairs and the kinetic processes involving these pairs in solution. Finally, we examine the main theme, the stereochemical aspects of radical pairs, and we consider the property of such pairs in solution, in solids, and in molecular aggregates such as biological membranes and micelles.

II. RADICALS AND RADICAL PAIRS

A. Radical Structure

Free radicals are classified according to their kinetic properties and also according to orbital occupation of the odd electron on the radical. Thus radicals are divided into two kinetic classes, transient and persistent (6). Transient species are those that undergo bimolecular self-reactions at the diffusion-controlled kinetic limit and persistent radicals are radicals that show kinetic stability.

Radicals are also differentiated as π or σ species by odd electron orbital occupation. Sigma radicals have an unpaired electron occupying an *sp* or sp^2 orbital. Pi-localized radicals are species bearing an unpaired electron localized in a single *p* orbital; in π-delocalized radicals the unpaired electron can delocalize to vicinal *p* orbitals.

The geometry of simple alkyl radicals has been a matter of considerable debate during the last decade. In 1972, Wood et al. (7) suggested that the *tert*-butyl radical is significantly pyramidal. This suggestion was based on the magnitude and temperature dependence of the ^{13}C hyperfine splitting in the EPR spectrum and was initially disputed on both experimental and theoretical grounds (8). In 1981, Paddon-Row and Houk carried out extensive calculations on the *tert*-butyl radical and reported that the degree of pyramidalization is approximately 40% that of a perfect tetrahedron and the barrier to inversion is on the order of 1–2 kcal/mole (9). Theoretical studies by Yoshimine and Pacansky confirmed these results and suggested that the *tert*-butyl radical structure corresponds to a nonplanar C_{3v} geometry (10). The deviation of alkyl radicals from planarity depends on substitution on the radical center with the methyl radical being planar and the ethyl, isopropyl, and *tert*-butyl being increasingly nonplanar in their minimum energy conformation.

It has been suggested that torsional strain is the primary structural feature responsible for the nonplanarity of 2° and 3° alkyl radicals. This is illustrated in Figure 1 with Newman projections for the isopropyl and *tert*-butyl radicals. Increasing substitution on the radical center increases torsional strain and this torsional strain can be minimized by pyramidalization at the radical center, as illustrated in Figure 1 for the *tert*-butyl radical.

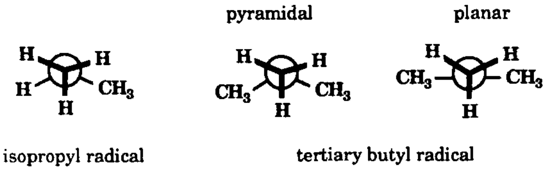


Figure 1. Newman projections of isopropyl and *tert*-butyl radicals.

Pi-delocalized radicals are thought to be planar. Thus radicals like allyl, cyanoisopropyl, propargyl, and benzyl maximize electron delocalization if the arrangement about the radical center is planar. In π-delocalized radicals, the conformation about the α-C–C bonds is important in determining radical delocalization and this results in sizable barriers to rotation about C–C bonds. For the allyl radical, as an example, rotation about the C–C bond, as measured by EPR, is 14 kcal/mole (11). This rotation corresponds to the allyl radical delocalization energy.

In summary, simple π-localized alkyl radicals are shallow pyramids with low barriers to inversion, while π-delocalized radicals are planar species.

B. Interconversion of Enantiomeric Radical Pairs and Radical Pair Dynamic Processes

The relative orientation of prochiral radicals in a radical pair controls the stereochemical outcome of coupling. Consider, for example, a prochiral cyano-substituted π-delocalized radical, **2**, paired with another radical, $\cdot R_3$, as shown in Figure 2. The stereochemical outcome of the coupling depends on whether $\cdot R_3$ adds to the *re*- or *si*-face of **2** and several molecular motions lead to interconversion of enantiomeric pairs.

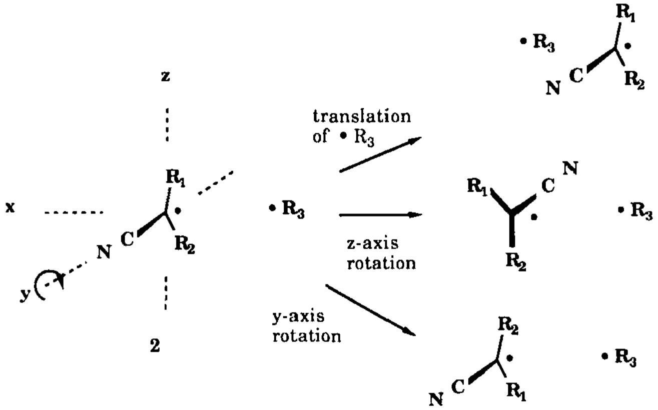


Figure 2. Reorientation of a prochiral radical.

Among the motions that interconvert radical pair enantiomers are translation of $\cdot R_3$ to the opposite face of the radical and rotation of **2** about the *y* or *z* axes. A similar analysis can be made of radical pairs made up of two prochiral radicals, such as **2**. In this case, each radical has a *re*- or *si*-face and coupling can yield diastereomers (meso and (±) diastereomers, if the two radicals in the pair are identical].

Consideration of the stereochemistry of π-localized radical pairs is complicated because inversion processes link enantiomeric radicals. Thus a nonplanar localized radical with three different alkyl substituents is chiral and inversion of the nonplanar radical interconverts enantiomers. It is thus possible for π-localized nonplanar radical pairs to undergo rapid inversion before coupling. Figure 3 shows a pair of chiral nonplanar radicals. The *S*/*R* radical pair is connected to the *S*/*S*, *R*/*R*, and *R*/*S* pairs by inversion of pyramidal radical centers. Of the four radical pairs shown in Figure 3, only the *S*/*R* radical pair is oriented so that it can couple to give products; the other pairs would have to undergo rotational or translational motions before coupling could occur. Analysis of this pair of nonplanar radicals is thus similar to analysis of the planar delocalized radicals shown in Figure 2, if it can be assumed that radical inversion processes are fast, relative to reorientation phenomena. If inversion is slow, relative to motions that reorient pairs, the determining process for product stereochemistry from such pairs would be radical inversion.

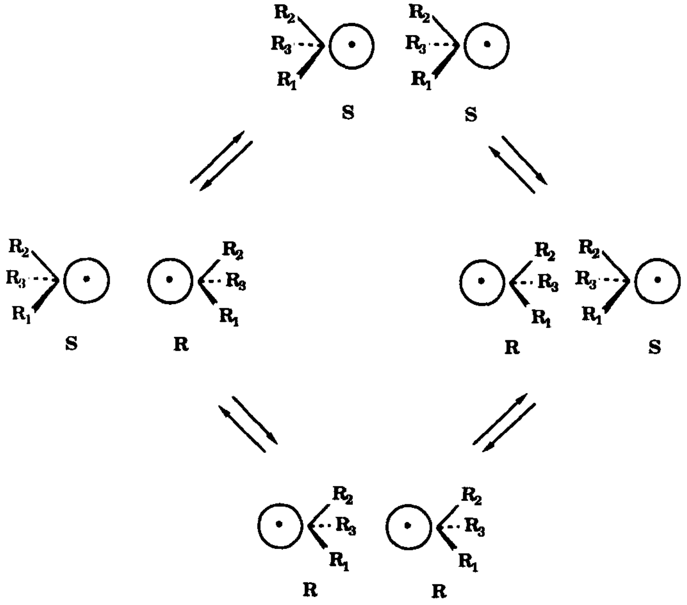


Figure 3. Reorientation of a chiral pair of nonplanar radicals.

A system for the study of radical pair stereochemistry must involve a precursor that generates the pair with given stereochemistry. Typical precursors for radical pairs are diazenes, peroxides, ketones (via Norrish I photofragmentation), carbenes (via H-atom abstraction), or hydrocarbons with weak C–C bonds. The processes important for radical pairs formed from diazene precursors are shown in Figure 4.

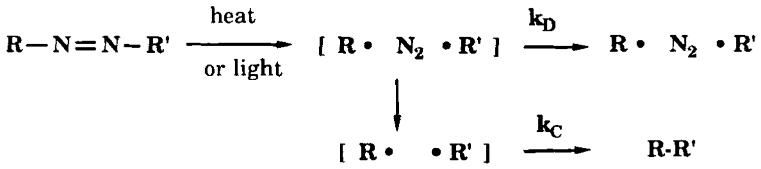


Figure 4. Reaction pathways for radical pairs from diazenes.

Once the pair is formed, diffusive separation (k_D) competes with coupling of the radicals. Diffusive separation of pairs of radicals leads to free radicals in solution and once the radical escapes its initial partner by this process, loss of stereochemistry is virtually assured. Consideration of radical pair stereochemistry thus involves the stereochemistry of the caged pair initially formed in the conversion (shown in brackets in Figure 4). Subsequent pairs formed after separation and reencounter will undoubtedly couple with a random stereochemical result. The stereochemistry of pairs of radicals generated from an azo precursor thus involves competition of reorientation phenomena, such as those described in Figure 2, with coupling and diffusive separation of the radical pair. If coupling is fast, relative to diffusion and reorientation, stereochemical retention of configuration from diazene to coupling product will result. If reorientation processes occur rapidly, compared with diffusion and coupling, stereochemical randomization will result. Finally, if diffusion is rapid, compared with other processes, no cage coupling products will iresult and coupling products formed will be the result of random encounters of radicals. These products will form with random configuration. In practice, one can limit the coupling products to cage products by scavenging radicals that escape from the initial solvent cage with typical free radical scavengers, such as thiols, nitroxides, or oxygen.

An alternate approach to the study of the stereochemistry of radical pair coupling is to generate the radicals separately and let random pair formation lead to the coupling product. Examples of this approach would be to form initiator radicals from a peroxide, **3**, as shown in Figure 5. After escape of alkoxyl radicals from their initial solvent cage (indicated by the brackets in Figure 5), the alkoxyl radicals abstract hydrogen from a substrate, R–H. The radical R•, in a secondary radical pair encounter, ultimately dimerizes, disproportionates, or couples with another radical. If R• is prochiral, diastereomeric coupling products R–R will be formed. This secondary encounter approach is different from the diazene kinetic product approach described in Figure 4, since the secondary radical pair is not generated with a particular stereochemical bias, while the initial encounter radical pair from diazenes, for example, may be formed as only one stereoisomeric entity. The secondary encounter approach will give information about (a) preferential formation of

$$\underset{3}{\mathrm{R'\text{-}O\text{-}O\text{-}R'}} \longrightarrow [\,\mathrm{R'\text{-}O}\bullet \quad \bullet\mathrm{O\text{-}R'}\,]$$

$$[\,\mathrm{R'\text{-}O}\bullet \quad \bullet\mathrm{O\text{-}R'}\,] \longrightarrow 2\mathrm{R'O}\bullet$$

$$2\mathrm{R'O}\bullet + \mathrm{R\text{-}H} \longrightarrow \mathrm{R}\bullet + \mathrm{R\text{-}O\text{-}H}$$

$$2\,\mathrm{R}\bullet \longrightarrow \mathrm{R\text{-}R}$$

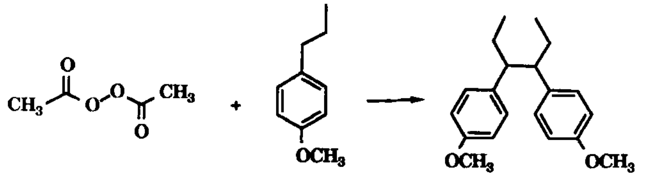
Figure 5. Radical pair products from secondary radical pair encounters.

one particular stereoisomeric radical pair in random radical encounters, or (b) relative energy barriers for stereoisomeric transition states in radical pair coupling.

III. RADICAL PAIRS IN SOLUTION

A. Kinetic Coupling

The stereochemistry of radical pairs and radical chain processes was reviewed by Eliel (12) in 1956. There are many reports of the secondary encounter approach to study radical pair coupling in the mid-1940s to the early 1960s. Most of the early reports use crystallization, distillation, or IR spectroscopy to analyze product mixtures and it was not until the late 1950s that GC techniques provided the powerful analytical tool necessary for this problem. The early reports nevertheless suggest that radical pair coupling by the secondary encounter approach leads, in most cases, to 50:50 stereoisomeric product mixtures (13–17). For example, Kharasch et al. decomposed acetyl peroxide, **4**, in *p*-methoxy propylbenzene, **5**, and isolated the stereoisomeric 3,4-diarylhexanes, **6**, by crystallization (see Figure 6). Nearly equal amounts of the stereoisomeric products are formed. Similar experiments suggested



4 **5** **6** (meso and ±)

Figure 6. Secondary radical encounter benzylic coupling.

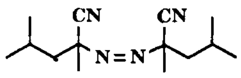
random coupling of 1-phenylhexyl radicals (18) and 1-phenyl-1-methylethyl radicals (13). In 1961, Axenrod carried out a careful GC analysis of a series of hydrocarbon radical coupling reactions and found some selectivity in the coupling mixture (19). The radicals and % meso coupling product are shown in Table 1.

Table 1
Diastereoselectivity in Coupling of α-Aryl Radicals by the Secondary Encounter Approach

Radical	% meso R–R	Temperature Range (°C)
$\text{Ph-}\dot{\text{C}}\text{H-CH}_3$	50.4 ± 0.4	20–135
$\text{Ph-}\dot{\text{C}}\text{H-CH(CH}_3)_2$	55.4 ± 0.4	68–172
$\text{Ph-}\dot{\text{C}}\text{H-C(CH}_3)_3$	57.4 ± 0.5	65–180

The meso coupling product is thus preferred in these reactions and this preference is enhanced by increasing the steric bulk of the alkyl radical substituent. It should be noted that similar selectivity of coupling is observed for radical generation by peroxide initiators or by generation of the radicals by reaction of an alkyl halide precursor with CH_3MgBr (19). This supports the notion of radical intermediates in Grignard coupling reactions. Other studies of the α-phenylethyl radical formed from diazenes (20) or peranhydrides (21) report a 50:50 meso: (±) product mixture. Thus both the initial and secondary radical encounter approaches suggest totally random coupling for this radical.

The cyanosubstituted diazene **7** was studied as a source of radical pairs by Overberger et al., and the coupling products are formed in an equimolar mixture, starting from either meso or (±) precursor (22). A stereochemically random conversion of **9**→**10** was also reported (23).



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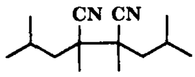

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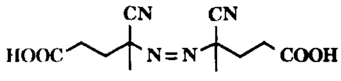

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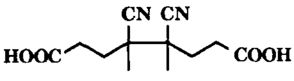

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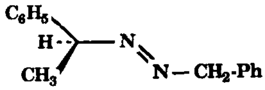
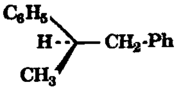
While hydrocarbon radicals thus appear to couple with a nearly random orientation, other radicals are reported to couple with significant diastereoselectivity. Thus Kharasch et al. (14) reported that acetyl peroxide and dimethyl succinate (**11**) react to give **12**, $\text{MeOOC–CH}_2\text{–CH(COOMe)–)}_2$, with a meso: (±) product ratio of 98:2. The radical $p\text{-OCH}_3\text{–C}_6\text{H}_9\text{–C}^{\bullet}\text{H–COOH}$ couples to give predominantly meso product (24) and the radical $\text{Ph-C}^{\bullet}\text{H–OCO–Ph}$ gives 85% meso coupling product (25). While these early studies appear to be unambiguous (particular those of Kharasch), it would be desirable to reexamine some of these systems with modern analytical tools.

Kopecky and Gillan studied the simple chiral diazene (−)-(*S*)-1,1′-diphenyl-1-methyl azomethane, **13**, and reported on the stereochemistry of radical pair coupling products formed in the decomposition of **13** (26). Table 2 shows product retention of the configuration of **14** formed under a variety of conditions for thermal decomposition of **13**. From these data, a simple expression for $(k_c/k_r)_{\text{cage}}$, the ratio of the rate of cage coupling of the radical pair to the rate of rotation (reorientational phenomena, as described in Figure 7) is calculated. Coupling is shown to be small relative to radical reorientation, ~0.06, and this results in very little transfer of stereochemical information from the diazene precursor to the coupling products.



(-)-*S*- **13**



14

Table 2
Stereochemistry of **14** Formed in Decomposition of (−)-(*S*)-**13**

Solvent	Temperature (°C)	$[\text{C}_4\text{H}_9\text{SH}]$ (*M*)	% Retention	$(k_c/k_r)_{\text{cage}}$
Benzene	110	0	5.6	
Benzene	110	1.2	10.3	0.06
Chlorobenzene	107	0	8.2	
Chlorobenzene	107	1.1	13.0	0.09

In 1970, Greene and co-workers reported on the stereochemistry for free radical recombination reactions with the use of pure (−)-(*S*, *S*)-azobisphenylethane, **15** (27, 28). Decompositions of *meso*- and (−)-(*S*, *S*)-azo diastereomers were carried out in the presence and absence of free radical

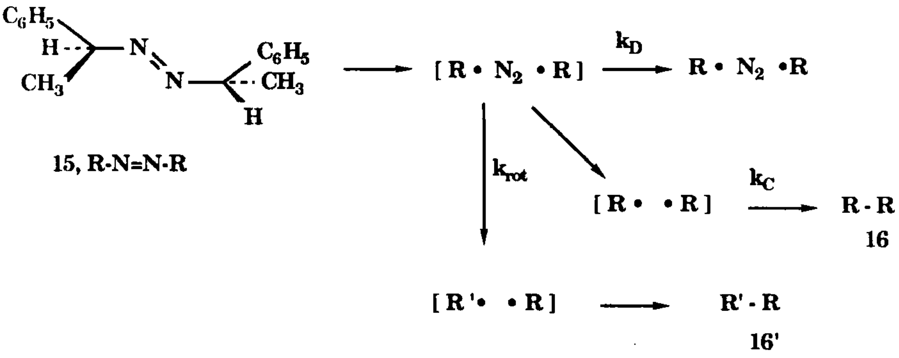


Figure 7. Reaction pathways for decomposition of **15**.

scavengers (Table 3). *Meso*- and non-*meso*-**15** gave similar amounts of the hydrocarbon coupling products and these products were formed in yields as high as 88% in the absence of scavengers. The mechanism for decomposition of **15** is shown in Figure 7. Yields of the coupling products dropped to 28% in the presence of scavengers (nitroso-*t*-butane, benzene, 110°C). This cage coupling product forms with a meso/non-meso ratio close to 1:1, indicating that reorientation is fast relative to radical coupling. Initial encounter radical pairs are shown in brackets and escape radicals are shown without brackets in Figure 7.

Table 3
Decomposition of Azobis-α-phenylethane, **15**. (Solvent Benzene at 105°C)

Diastereomer **16**	Scavenger	Non-Meso/Meso Product
(−)-(*S*,*S*)	None	1.01
meso	None	0.99
(−)-(*S*,*S*),	PhSH	1.11
meso	PhSH	0.89

Greene calculated k_{rot}/k_{comb}, the rate of rotation of one radical relative to its partner compared with the rate of recombination of the radical pair, and concluded, as did Kopecky, that reorientation phenomena in solution are fast relative to coupling processes. The probability of radical rotation occurring prior to coupling, x, was 0.45 in the Greene et al. study, while Kopecky and Gillan found $x = 0.44$ in their system.

Koenig and Owens utilized peroxide initiators to study radical pair reorientation phenomena (27, 28). The peroxyester (+)-(*S*)-*tert*-butylperoxy-2-methylbutyrate, **17**, was used as a source of optically active 2-butyl:*tert*-butoxy radical pairs, as shown in Figure 8. The yield of coupling product **18** and its optical purity is dependent on solvent viscosity. For example, decomposition of **17** in decane resulted in 16% of product **18** with 1.7% optical purity, while decomposition in more viscous paraffin oil gave **18** in 29% and with optical purity of 6%. Koenig analyzed k_t/k_c for this system (k_t = rate of radical tumbling) and found it to be solvent dependent and much larger than the values found by Kopecky for α-methyl-benzyl radicals. Thus k_t/k_c for pairs formed from **17** was 23 in paraffin oil and as great as 200 in decane. This value is over 10-fold greater than values found by Kopecky for the benzyl radical pairs. Radical scavengers had little, if any, effect on the optical purity and yields of ether formed from **17**, indicating that no significant amount of ether is formed via random combination of radicals that may have escaped the initial radical cage. Koenig and Owens differentiate overall tumbling of the 2-butyl radical (k_t) from internal rotation about the ethyl substituent, k_r. The tumbling motion is sensitive to solvent fluidity, while k_r is not.

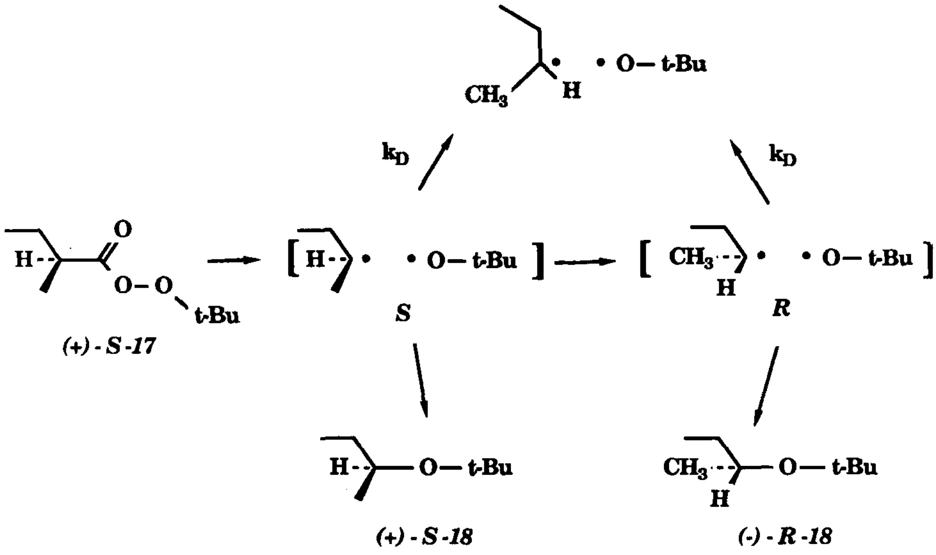


Figure 8. Pathways for decomposition of perester 17.

Overberger and Labianca (29) studied the photochemical decomposition of (+)-4,4′-azobis-(4-cyanopentanoic acid), **19**. This molecule is of interest in comparison to the systems of Greene and Kopecky because of the possibility of hydrogen bonding effects on the radical pair. Products of photodecomposition are shown in Figure 9. Two diastereomeric diacids **21** are formed and are optically inactive, while the monoacid **20** is formed optically active. In fact, the only optically active product of photolysis was found to be **20**. This result was rationalized on the basis of an azo trans–cis photoisomerization, followed by a reverse ene-type reaction, as shown in structure **22**. This concerted process may be facilitated by hydrogen bonding from the carboxylate to the azo linkage.

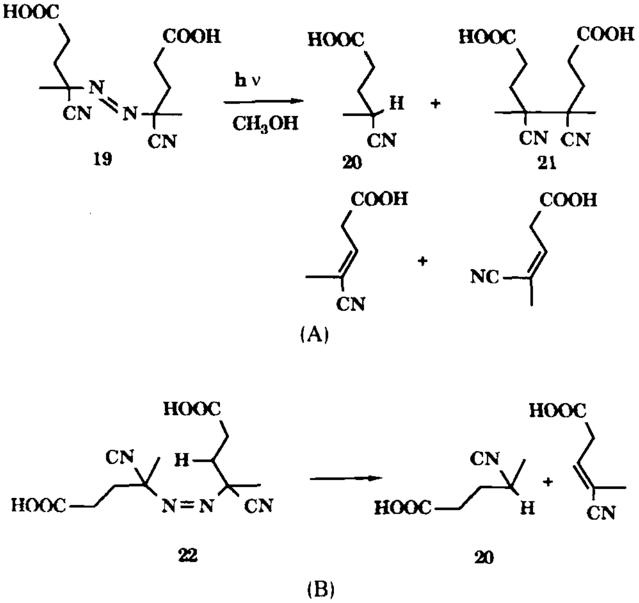


Figure 9. (*A*) Products from photolysis of **19**. (*B*) Proposed intermediate leading to **20**.

All of the solution radical pair studies considered thus far generate radical pairs separated by a third molecule, such as nitrogen (diazenes) or CO_2 (peresters). Lee et al. (30) studied pairs of radicals generated from ketenimines **23**, as shown in Figure 10.

The radical pair generated from **23** is not separated by a third molecule and the data suggest that k_r/k_c is much lower in this system than for the comparable diazene systems. The value of radical rotation relative to coupling (k_r/k_c) is 0.4 in CCl_4 solvent and 0.8 in acetonitrile. This translates to a rotational probability $x=0.23$ compared to $x=0.44$ in pairs of radicals generated from diazenes (see above). Singer et al. suggested that "proximate

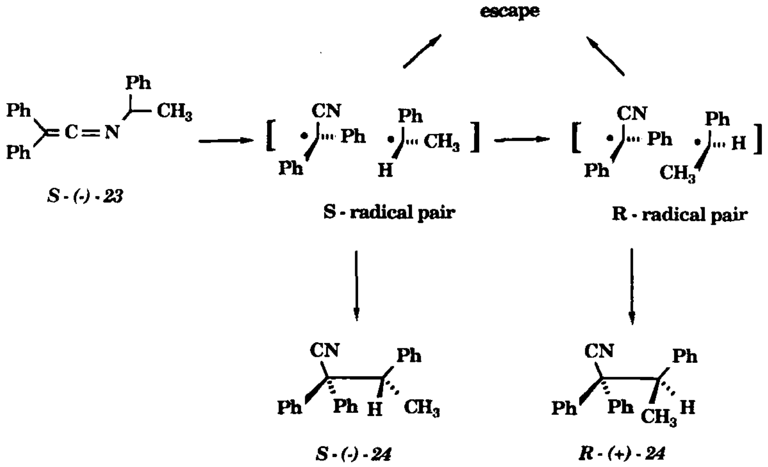
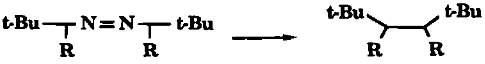

escape
Ph
CH3
C=N
Ph
Ph
S-(-)-23
CN
Ph
Ph
CH3
H
S - radical pair
CN
Ph
Ph
Ph
H
CH3
R - radical pair
CN
Ph
Ph
Ph
H
CH3
S-(-)-24
CN
Ph
Ph
Ph
CH3
H
R-(+)-24

Figure 10. Thermal decomposition of a chiral ketenimine.

radicals," such as those generated from the ketene, couple more rapidly than nonproximate radicals generated from diazenes and peresters. This faster coupling for proximate radicals results in less rotation and consequent loss of configuration.

In an elegant series of publications, Rüchardt and his collaborators reported on radical coupling to form highly hindered products (31). Azo compounds **25a–d** were decomposed thermally and photochemically and diastereoselectivities of radical coupling were determined over a temperature range of 150°C.

The data indicate significant selectivity for coupling of radicals from **25c** (±/*meso*-**26c** = 1.65) and **25b** (±/*meso*-**26b** = 0.45). Coupling from radicals formed from **25a** was less selective and **26d** was formed from the azo precursor in essentially a 1:1 mixture of meso and (±) diastereomers. The product distribution is independent of temperature and solvent viscosity.


t-Bu
N=N
t-Bu
R
R
t-Bu
t-Bu
R
R

25 a. R = C_6H_5 **26**

b. R = 4-t-Bu-C_6H_4

c. R = 4-Cl-C_6H_4

d. R = CH_3

The purely aliphatic radicals formed from **25d** led to no diastereoselectivity in coupling, while radicals with aromatic substituents gave selectivity in product formation and this has led Rüchardt to suggest aromatic radical pair complexes as the primary source of product control in these systems. Both (±) and meso radical complexes may form and the entropy content of these complexes must influence stereoselectivity in the coupling step.

B. Radical Pair Coupling Equilibria

It should be noted that highly substituted systems like those studied by Rüchardt and his group, and also highly stabilized radicals, potentially provide a means of establishing equilibria between coupling product diastereomers. In the case of **26c**, the (±)diastereomer is some 2.55 kcal/mole more stable than *meso*-**26** and these strained compounds are unstable with respect to the radical pair at temperatures near 300°C. This equilibrium (shown in Figure 11) provides, at least in theory, a means for equilibrating coupling product diastereomers. In practice, this equilibrium is obtained only if the intermediate radicals do not react by any other pathways except combination. In fact, a systematic study of such radical pair formation by C–C homolysis has led to a new understanding of the nature of the carbon–carbon bond (32).

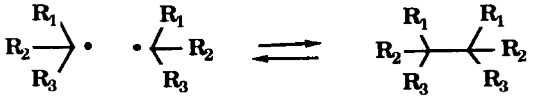
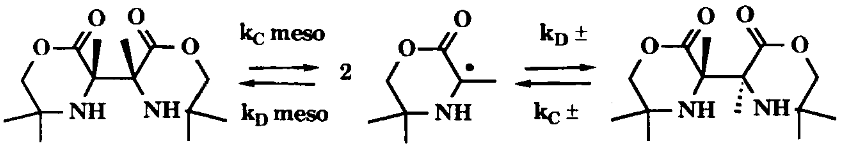


Figure 11. Equilibration of stereoisomers via radical pairs.

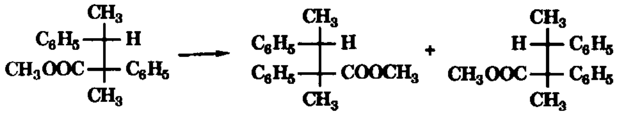
It should be emphasized that the diastereomeric product distribution that results from dimer–monomer equilibration of stabilized radicals is controlled by different factors than the kinetically controlled couplings we have previously discussed. As an example, the meso and (±) dimeric products **28** are formed by coupling of the stabilized capto-dative radical **27**. The equilibrium constant at 30°C between the meso and (±) dimer is 2.2 (33). This equilibrium constant depends on k_C and k_D for (±) and meso, while the product



meso-**28** **27** **(±)-28**

distribution obtained in azo compound decomposition is kinetically controlled, depending only on the relative k_C (±) and k_C meso rate constants (34). In the case of the radical **27**, incidentally, radical coupling proceeds with negative activation enthalpies and this may be understood by either an intermediate H-bonded radical pair complex, or by a rapidly rising $-T\Delta S$ term (35).

In a recent study, Doering and Birladeanu reported on rotational preference in cage dissociation–recombination (36). These workers studied the automerization of optically active methyl-*threo*-2,3-diphenylbutane-2-carboxylate, **29**. The compound 9,10-dihydroanthracene was used to scavenge radicals that escaped the initial solvent cage and automerizations were


2S, 3S-**29** (*Threo*) *2R, 3S*-**29** (*Erythro*) *2S, 3R*-**29** (*Threo*)

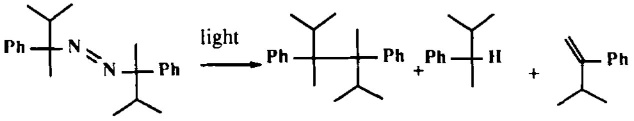
carried out by thermolysis of **29**-*threo* in *o*-dichlorobenzene at 300°C for 30 min. *Erythro*-**29** is recovered from this reaction mixture 28% optically pure, the 2*S*,3*R* stereoisomer being preferred. These data suggest that the α-phenylethyl radical undergoes rotation preferentially over the α-carbomethoxy-α-phenylethyl radical. That is, thermolysis of **29**-*threo* leads to a "proximate" radical pair that can lose configuration. Rotation of the phenylethyl radical in this pair apparently occurs much more readily than rotation of the larger partner radical ($\Delta\Delta G^{\neq}$ ~0.65 kcal/mol).

In summary, it can be concluded that reorientation motions (rotation, tumbling) of radical pairs in solution are generally faster than coupling of the radicals. Viscous solvents may cause somewhat greater retention of configuration due to the sensitivity of radical tumbling on solvent viscosity, but retention of configuration in solution is small, even with viscous solvents.

IV. RADICAL PAIRS IN SOLIDS

The initial studies in this field came from Bartlett and McBride, who studied the photodecomposition of *meso*- and (±)-azobis-(2-phenyl-3-methyl-2-butane), **30**, in a methylcyclohexane glass at −196°C (37). They reported that *meso*-**30** gave only the meso coupling product **31** and that (±)-**30** gave only the (±)-**31** compound. It was concluded from these results that these radical pairs were produced in a cavity of fixed structure and that this cavity enforces retention of configuration on the pair. That is to say, rotation and tumbling processes are forbidden in the cavity and coupling dominates kinetically to give the product with retained stereochemistry. In subsequent studies, the disproportionation product **32** was also shown to have significant optical activity and it was concluded that retention thus predominated in both coupling and disproportionation within the glass cavity (38).

Organic reactions in crystalline matrices have received extensive study and the chemistry of radical pairs generated in crystals has recently been reviewed (39). The "topochemical principle" has frequently been invoked to explain the reactivity of substrates in crystals and this principle applies to the study of **30** (Figure 12). This principle is essentially a least-motion argument (40), which states that reactions in solids should take place with minimum atomic and molecular motion.



30 **31** **32**

Figure 12. Photolysis in a glass.

McBride has pointed out, however, that the topochemical cavity may be formed with local stresses, which bias normal radical pair reactions by imposing "tens of thousands of atmospheres" of internal pressure (39). Decomposition of acyl peroxides in the crystal, for example, generates CO_2, which may cause local stress. This local stress may direct reactions of radical pairs away from least motion pathways, thus violating the "topochemical principle" in these systems. Several examples of this "local stress" phenomenon have been described.

Zayas and Platz (41) have applied the "topochemical principle" to account for the behavior of diphenylcarbene in polycrystalline (+)-(*S*)-2-butanol. Photolysis of diphenyldiazomethane in (±)-2-butanol and in (+)-(*S*)-2-butanol at 77 K gave products **33**–**38** in the yields shown (Figure 13). A product temperature dependence was observed and the yields of **34**, an insertion product at the stereocenter, were as high as 60% at 137 K. Product accountability increased from about 35% at 77 K to >95% at 137 K. It is suggested that diphenylcarbene must have enough mobility at 137 K to distinguish the various C–H bonds in 2-butanol and abstract the weak tertiary C–H bond of the matrix to give the most stable radical pair (and ultimately **34**). At lower temperatures, the motion available to the carbene is much more restricted and the chemistry is apparently dominated by random hydrogen abstraction.

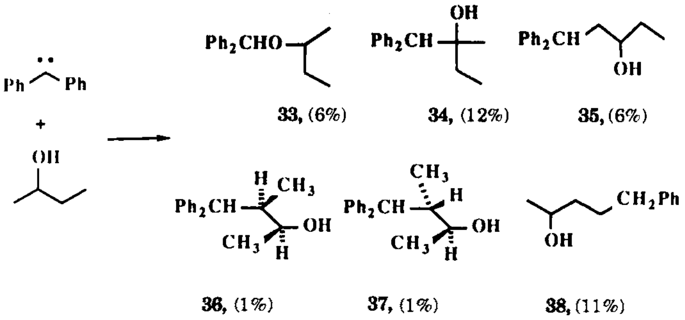
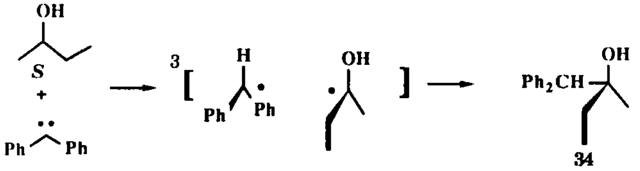


Figure 13. Diphenylcarbene insertion at a chiral center.

Photolysis of diphenyldiazomethane at 77 or 137 K in solid (+)-(*S*)-2-butanol yielded the product alcohol **34** with retained stereochemistry. Analysis of **34** formed in this way indicates the presence of only one enantiomer when chiral shift reagents are utilized. The specific rotation of the products reported indicates that **34** isolated is not optically pure (an apparent inconsistency with the chiral shift study), but that it nevertheless is formed with substantial retention of configuration. These results can be interpreted by a triplet carbene abstracting the tertiary hydrogen to give a triplet radical pair. This triplet pair formed in a polycrystalline cavity collapses (presumably after spin inversion) to give the coupling product **34** with stereochemical retention.

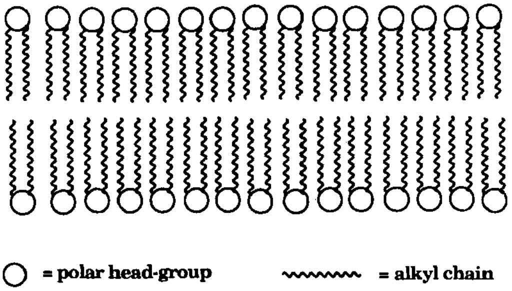


V. RADICAL PAIRS IN MOLECULAR AGGREGATES

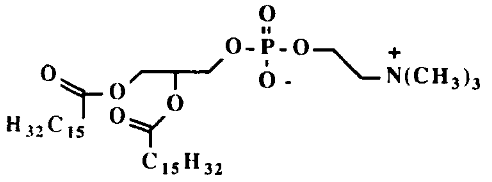
A. Micelles and Bilayers

Amphiphilic molecules (with polar-hydrophilic and nonpolar-hydrophobic moieties) self-aggregate such that their nonpolar groups are sequestered from water, while the head groups remain solvated by the water at the surface of the aggregates (42). Self-aggregation occurs when the concentration of the amphiphile exceeds the critical micelle concentration (CMC). Each amphiphile has a characteristic CMC, which is determined by the length of the hydrophobic group and the size and number of polar head groups. It appears that micelles are dynamic species and intermicellar exchange of constituents is rapid. Several models of micellar structure have been proposed, but the nature of these dynamic aggregates is still a matter of current debate (43, 44). Micelles are generally formed from amphiphiles having one polar head group per hydrophobic alkyl chain. Sodium dodecyl sulfate (SDS) and cetyl trimethylammonium bromide (CTAB) are examples of molecules that form micellar aggregates in water.

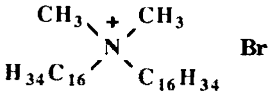
When amphiphiles having two alkyl chains are raised above their gel-to-liquid crystalline phase transition and vortexed in aqueous solution, the usual result is an emulsion of bilayers called multilamellar vesicles (MLVs) or liposomes. An MLV has layers of bilayers separated by layers of water in an onion-like arrangement. A schematic bilayer is shown below. When MLVs are sonicated, ULVs are formed. A ULV (unilamellar vesicle) has one lipid bilayer enclosing an aqueous compartment. The ULVs are unstable and slowly aggregate to MLVs.



Both MLVs and ULVs (liposomes) are the most commonly used model membranes. The phospholipid dipalmitoylphosphatidylcholine (DPPC), for example, forms MLVs and ULVs in aqueous media and is an example of one molecular species of biological importance, phosphatidylcholines having the common name of lecithin, and DPPC itself being an important lung surfactant. Other amphiphiles that form bilayers are known; one that is particularly well-studied is dicetyldimethylammonium bromide (DDAB) (45–49).



DPPC



DDAB

The course of chemical reactions may be altered when they proceed in micellar systems, as opposed to isotropic media. These differences can generally be attributed to the environment created at the interface of the two phases—aqueous and organic. Amphiphilic solutes experience enhanced local concentrations relative to the bulk phase and this may hasten second-order reactions between such solutes. Amphiphiles tend to orient in aggregates and this sometimes affects the stereochemical course of a reaction. Finally, the interface area is highly polar and reactions of solutes localized there may be accelerated because of this polarity. Thus micelles and other aggregates may be catalytic in that they can accelerate reactions without themselves being altered. During the past 20 years there has been extensive investigation of micellar catalysis (50–52).

B. Free Radical Reactions in Molecular Aggregates

Free radical initiators have been studied in micelles and liposomes. Most of these studies were carried out because of the importance of free radical autoxidation in biological membranes. A means for initiating autoxidation in a controlled way was necessary, and for that reason several initiators have been examined in aggregates, such as micelles and liposomes. The general scheme of radical initiation is shown in Figure 14. After extrusion of nitrogen, the remaining radicals can either escape their solvent cage and be scavenged by oxygen, or they can remain trapped in the cage and give combination or disproportionation products. The efficiency of escape from the solvent cage (e) can be defined as in eq. [2] and the efficiency can be determined by measuring the rate of consumption of inhibitors that trap ROO•and comparing this rate to the rate of decomposition of the diazene. The initiator di-*t*-butylhyponitrite (DBHN) gives an efficiency of radical production of 0.66 in chlorobenzene, while the value of e drops to 0.30 in 0.5 *M* SDS micelles (53). The same initiator gives e = 0.09 in DPPC liposomes (54). It should be noted that DBHN gives alkoxyl radicals upon decomposition and these oxyl radicals do not react with oxygen before being trapped by inhibitors. The low escape efficiency found for DBHN in liposomes falls in line with the results of every other mechanistic probe of the structure of the microenvironment of

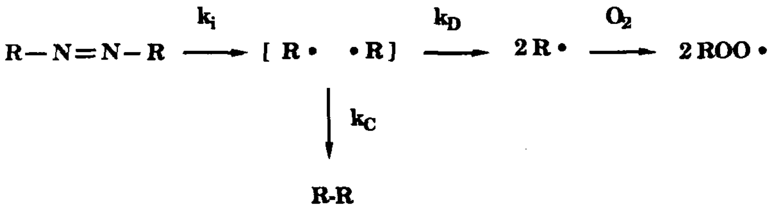
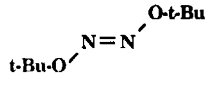


Figure 14. Kinetic scheme for diazene decomposition.

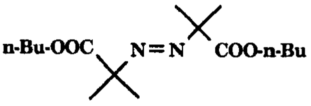
membrane interiors. The hydrophobic region of the lipid bilayer, however ordered or disordered, is very viscous.

$$\frac{k_D}{k_D+k_C}=e \qquad [2]$$

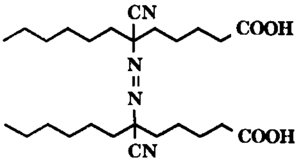
Mill and co-workers have also studied membrane oxidation and have used azobis[2-(2*n*-butylcarboxyl)propane] (ABCP) as an initiator (55). They find escape efficiencies of 0.2–0.25 for this initiator in phospholipid liposomes and these values imply a lower viscosity for membranes than the studies with DBHN.



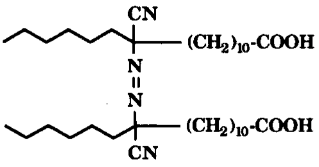
DBHN



ABCP



meso and ± 39, (6,6')



meso and ± 40, (12,12')

We have prepared the diazenes **39** and **40**, which are analogous to the familiar free radical initiator AIBN (56, 57). We equipped these diazenes with hydrophilic and hydrophobic groups, thus making them amphiphilic and also introducing stereochemistry into the molecules. It was our intention to utilize these initiators to study membrane-phase autoxidation and we thus began a thorough examination of their behavior as initiators.

There is a concern as to whether the diazenes **39** and **40** incorporate into liposomal bilayers formed from phospholipids. X-Ray diffraction has been used to study the structure of bilayers and this technique affords information regarding the position and orientation of molecules in bilayers. When **39** or **40** is placed in aqueous DPPC at 20°C (pH 7), low angle X-ray analysis suggests that the diazene is associated with liposome. No new phases are observed, the bilayer loses its chain tilt, and the head group to head group repeat distance increases from 43 to 47 Å, consistent with incorporation of a carboxylate in the bilayer.

The efficiencies for decomposition of the amphiphilic initiators **39** and **40** are "normal" in isotropic solution at 60°C (AIBN = 0.6). These efficiencies are

Table 4
Efficiencies of Diazene Radical Production

Diazene	e in C_6H_5Cl	e in DPPC Liposomes
meso-**39**	0.51	0.05
(±)-**39**	0.60	0.04
meso-**40**	0.48	0.08
(±)-**40**	0.51	0.07

presented in Table 4 for chlorobenzene solvent and also for DPPC liposomes. The efficiencies obtained for these diazenes in liposomes are the lowest reported in these aggregates and indicate a viscous environment for these initiators (57).

Diastereomeric differentiation in rates of diazene decomposition was demonstrated. Decomposition of *meso*- and (±)-**39** in chlorobenzene (0.002 *M*) showed that the meso compound decomposed 1.5 times faster than the (±) diastereomer at 60°C. The greatest diastereomeric kinetic differentiation is seen when **39** was decomposed in aqueous emulsions (pH 7) of DPPC as multilamellar vesicles. A rate ratio meso/(±) of 6.5 was observed under these conditions (56). It should be noted that the meso and (±) dimethyl esters of **39** undergo decomposition at 60°C in chlorobenzene with identical rates. There is thus no apparent differentiation of the diastereomers of **39** as their dimethyl esters in isotropic fluids, but the liposomal binding of the diastereomeric diacids leads to kinetic differentiation of these compounds.

The diazenes form soapy solutions in pH 10 buffer and CMCs have been measured for *meso*- and (±)-**39**. The CMCs measured by surface tension are $1.3\ (\pm\ 0.1) \times 10^{-3}\ M$ for *meso*-**39** and $6.0\ (\pm\ 0.2) \times 10^{-4}\ M$ for (±)-**39**. The aggregates have not been further characterized (58).

The major products of decomposition of *meso*- and (±)-**39** are shown in Figure 15. The stereochemical assignment of the succinodinitriles, **41** (SCDN), was made by photolysis of the known (±)-**39** in a methylcyclohexane/ether glass at −196°C. Only one product was observed in this photolysis and this product was assigned the (±) stereochemistry. The dialkyl peroxides, DAP, were not assigned stereochemistry and these compounds are always formed in a 1:1 meso/± product ratio.

The retention of stereochemistry in the conversion of **39** to **41** was studied in isotropic fluids, in liposomes, and in micelles formed from the diazenes. Photolysis (23°C) or thermolysis (60°C) of the dimethyl ester of **39** in chlorobenzene leads to extensive loss of configuration in the product succinodinitriles **41**. Thus photodecomposition of *meso*-**39** dimethyl ester at

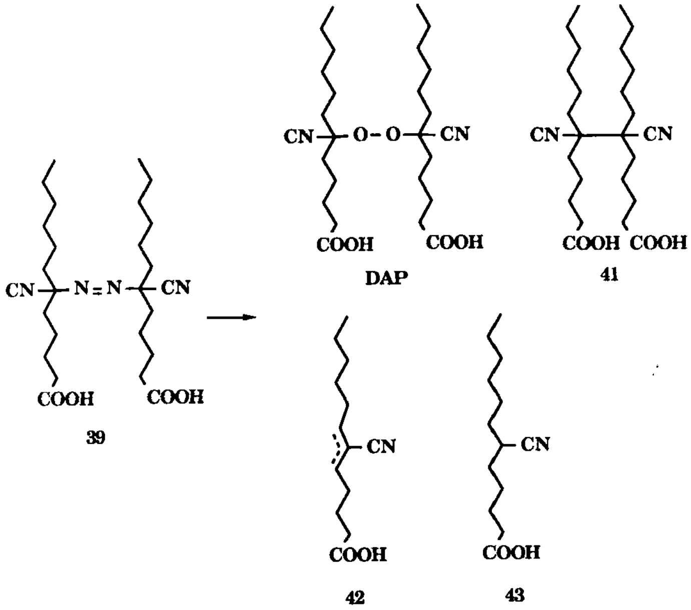


Figure 15. Products formed in the decomposition of **39**.

22°C gives a **41**-*meso*/(±) product ratio of 1.05. These results are analogous to those cited earlier by Greene and Kopecky (26–28) and indicate typically rapid rates of radical rotation relative to coupling.

Diastereomeric diazenes were photolyzed in MLVs of DPPC and the products were analyzed to determine diastereoselectivity in the conversion (59). These results are summarized in Table 5 and they are in striking contrast to the data obtained for decomposition of **39** in isotropic fluids. The (±)-diazene gives (±)/*meso*-**41** product ratios of over 6/1, while the meso compound decomposition occurs with generally lower diastereoselectivity [meso/(±)≈3/1]. This corresponds to a rotational probability before coupling of $x=0.07$ for the radical pair formed from the (±) precursor, while the pair formed from the meso precursor has $x=0.20$. It is apparent from these data that DPPC liposomes are a more constrictive environment for radical pair reorientation than isotropic fluids ($x=0.45$).

Photolysis of diastereomeric diazene diacids **39** in pH 10 buffer was carried out at various concentrations of diazene. The results are summarized in Table 6. Diastereoselectivity is expressed as the product ratio of the succinodinitrile products, **41**, and as diastereomeric excess, % DE. Yields for **41** and DAP are also reported.

Table 5

Diastereoselectivity of Radical Recombination in Phospholipid Vesicles

	Decomposition of *meso*-**39**		Decomposition of (±)-**39**	
	meso/(±)[b] **41**	% DE[c]	(±)/*meso*[b] **41**	% DE
29°C $h\nu$	2.33±0.71	40 (meso)	6.23±0.65	72 (±)
39°C $h\nu$	3.03±0.60	50 (meso)	6.05±0.15	71 (±)
49°C $h\nu$	1.96±0.43	32 (meso)	—	—
59°C $h\nu$	1.69±0.22	26 (meso)	6.00±0.86	71 (±)
60°C Δ	1.28±0.14	12 (meso)	5.24±0.25	68 (±)
70°C Δ	0.92±0.07	4 (±)	3.74±0.47	58 (±)
80°C Δ	0.96+0.07	2 (±)	1.84±0.46	30 (±)

[a] All data from decomposition of diazene **39** in DPPC.

[b] Mean (±) standard error.

[c] DE = diastereomeric excess with the predominant diastereomer indicated in parentheses.

Table 6

Diastereoselectivity for Decomposition of **39** in pH 10 Buffer for Photolysis of the Diazene Diacid at 22°C

Concentration	SCDN,[b] **41**	% DE[c]	% SCDN[d]	% DAP[e]	% Total[f]
		meso-**39**			
2.0×10^{-1} *M*	2.40±0.03	41.2±0.3	30	29	59
1.0×10^{-1} *M*	2.40±0.13	41.2±2.2	33	31	64
5.0×10^{-2} *M*	2.32±0.01	39.6±0.2	31	34	65
1.0×10^{-2} *M*	2.40±0.08	41.2±1.6	32	35	67
7.0×10^{-3} *M*	2.69±0.06	45.7±0.9	32	37	69
6.0×10^{-3} *M*	3.03±0.04	50.3±0.3	33	34	67
5.0×10^{-3} *M*	3.08±0.06	51.0±0.4	34	40	74
3.5×10^{-3} *M*	3.41±0.01	54.8±0.1	29	39	68
3.0×10^{-3} *M*	3.50±0.04	55.5±0.4	17	36	53
1.0×10^{-3} *M*	3.53±0.03	55.9±0.2			
9.0×10^{-4} *M*	3.52±0.02	56.0±0.3			
1.0×10^{-4} *M*	3.49±0.03	55.5±0.4			

(*continued*)

Table 6 (Contd)

Concentration	SCDN,[b] **41**	% DE[c]	% SCDN[d]	% DAP[e]	% Total[f]
		(±)-**39**			
$1.0\times10^{-1}\,M$	6.20±0.15[g]	72.2±1.0[h]	36	32	68
$2.5\times10^{-2}\,M$	5.82±0.04	70.7±0.5	37	35	72
$1.0\times10^{-2}\,M$	5.85±0.03	71.0±0.2	37	34	71
$4.0\times10^{-3}\,M$	4.81±0.10	65.1±0.5	34	32	66
$3.5\times10^{-3}\,M$	4.45±0.03	63.0±0.3	40	37	77
$3.4\times10^{-3}\,M$	4.44±0.16	63.2±0.4	45	37	82
$3.0\times10^{-3}\,M$	4.14±0.08	61.1±0.5	42	38	80
$2.5\times10^{-3}\,M$	4.00±0.13	60.1±0.9	38	40	78
$2.0\times10^{-3}\,M$	3.52±0.05	55.7±0.5	34	39	73
$1.5\times10^{-3}\,M$	3.45±0.10	55.0±1.1	41	37	78
$1.0\times10^{-3}\,M$	3.55±0.03	56.0±0.3			
$1.0\times10^{-4}\,M$	3.48±0.07	55.3±0.4			
$1.0\times10^{-5}\,M$	3.45±0.10	55.0±0.8			

[a] All data from photodecomposition of diazene diacid **39** at 22°C.
[b] SCDN = [*meso*-**41**/(±)-**41**] ± standard error.
[c] DE = diastereomeric excess of *meso*-**41** ± standard error.
[d] SCDN is the percent yield of the **41** recovered from each photolysis.
[e] % DAP is the percent yield of DAP recovered from each photolysis.
[f] Total yield recovered.
[g] SCDN = [(±)-**41**/*meso*-**41**] ± standard error.
[h] DE = diastereomeric excess of (±)-**41** ± standard error.

At high dilution, significant diastereoselectivities are seen in the SCDN product ratios from both meso and (±) diazenes; the original stereochemistry being preferred by a ratio of about 3.5 to 1. Figure 16 illustrates that above a certain concentration, significant changes in diastereoselectivity take place. The (±) diazene showed steadily increasing retention of stereochemistry, leveling off at a factor of about 6 to 1 at highest concentration. The meso diazene showed steadily decreasing retention of stereochemistry to about 2 to 1 at highest concentration.

C. The Relation of Observed Diastereoselectivity to Aggregation

No stereochemical retention is observed in the photolysis products from the dimethyl esters of **39** in chlorobenzene. This is indicative of no inherent

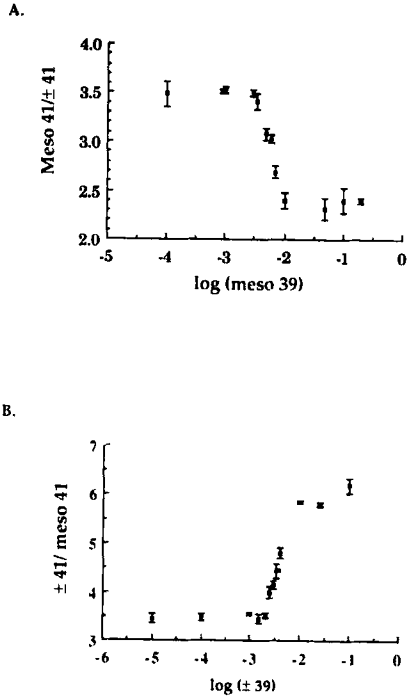
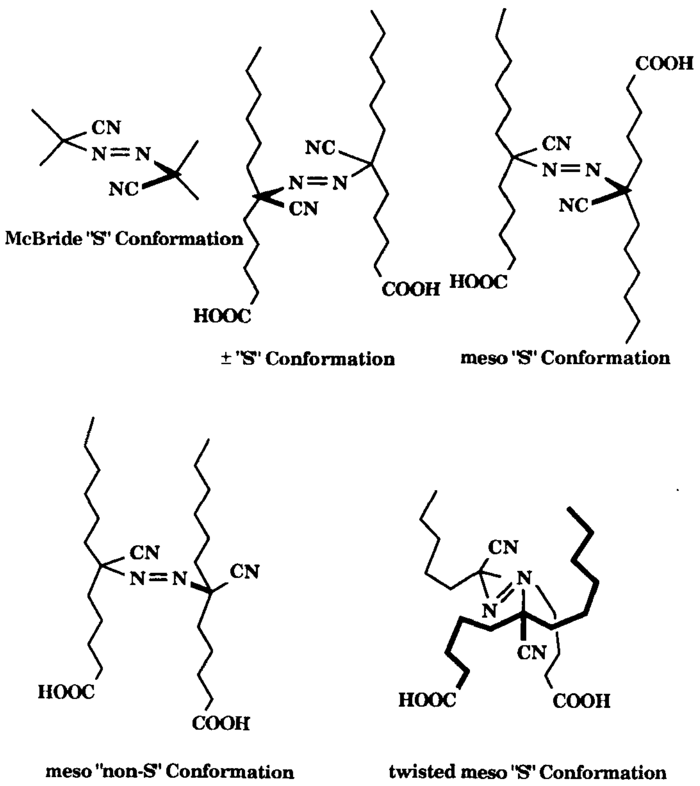


Figure 16. (*A*) Ratio of succinodinitrile (SCDN) products **41** (*meso*/±) versus log concentration of *meso*-**39** diazene precursor. (*B*) Ratio of SCDN products **41** (±/*meso*) versus log concentration of (±)-**39** diazene precursor.

intermolecular or intramolecular force, which binds the radicals formed from expulsion of nitrogen so that they can couple with retained configuration before they escape the initial encounter.

Radical pair mobility is reduced significantly by two forces in the case of the diacids at high dilution in water. These forces are not present in the radical pair generated by the dimethyl esters in chlorobenzene. Specifically, the increase in stereoselectivity observed with the diacids compared with the methyl esters is due to the hydration of the carboxylate head group or the lipophilic attraction of the hydrocarbon chains. These interactions drastically reduce the mobility of the radical pair and influence the stereochemical outcome of the coupled product.

As aggregation commences with increasing concentration, an added degree of orientation is added. Most of the polar acid head groups must orient themselves toward the interface with water. The lipophilic hydrocarbon chains would align themselves more or less parallel to each other. The



McBride 'S' Conformation

± 'S' Conformation

meso 'S' Conformation

meso "non-S" Conformation

twisted meso 'S' Conformation

Figure 17. Possible conformations of (±) and meso diazenes.

possible conformations of the diastereomers are seen in Figure 17. The (±) isomer arranges itself with the cyano dipoles trans to each other, giving nearly perfect C_2V symmetry around the vertical axis between the two hydrocarbon chains. Arrangement in this manner would allow ideal extended intermolecular packing. This is exemplified by the low CMC. Single crystal X-ray analysis of the prototype diazene azobisisobutyronitrile, AIBN, has been accomplished by Jaffe et al. (60). It was found that AIBN was staggered in an S-shaped arrangement, as is proposed for the (±) isomer (Figure 17). This conformation also allows a maximum anomeric interaction between the carbon–cyano bonds and the nitrogen lone pairs of the diazene.

However, in the case of the meso diazene, the *S*-conformation cannot be maintained, as in the case with the (±) isomer, and still place the head groups at the interface maintaining the parallel chains. There are two possible orientations that the meso diazene can adopt. The first allows the polar head groups to be placed at the interface, but maintains a non-*S* arrangement. This allows the carboxylate head groups to be placed at the ends of parallel chains and demands a conformation where the cyano groups are side by side with parallel dipoles. The second orientation maintains the *S*-arrangement and also allows the carboxylate chains to bend, bringing both carboxylate groups to the polar interface. This "twisted conformation" would result in increased gauche interactions in the carbon chains and would only be adopted if such interactions cost less energetically than what was gained from maintaining the presumably more stable *S*-diazene conformation. From our data, it is not possible to choose from these two possibilities.

Thus the (±) isomers are oriented in an optimum position for retention of stereochemistry once the radicals are formed in the aggregated DPPC or in micelles. However, the meso isomers resist such an ordered state relative to the (±). Aggregates that include the meso diazene are therefore packed less tightly and the radical pair loses stereochemistry more easily once formed. Randomization occurs to a certain extent with both diastereomers upon expulsion of nitrogen, but it is more prevelant for the meso isomer.

VI. SUMMARY AND FUTURE PROSPECTS

The dynamics of radical pair reactions in isotropic fluids is such that pairs of radicals generated with a defined configuration from a chiral precursor lose configuration before coupling occurs. This behavior of radical pairs has led to the generally held belief that all reactions proceeding through radical intermediates do so with loss of stereochemical configuration. While radical reactions do proceed with predominant loss of configuration in isotropic media, this is not the case for radical reactions in crystals, glasses, or molecular aggregates such as micelles and lipid bilayers.

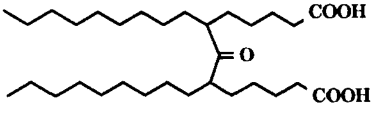
The "topochemical principle" may frequently be used to explain radical pair reactions in glasses and other matrices such as micelles and bilayers. This principle states that reactions occur with least motion in these aggregates and predicts that maintenance of stereochemical configuration is preferred in such media. Application of this principle is not universal, however, and examples exist where local stresses imposed by generation of radical pairs and other small molecules such as CO_2 in a topochemical cavity lead to non-least-motion products. These examples are observed for reactions in crystals or glasses and one expects that the "local stress" argument would not apply in more fluid liquid-crystalline media such as lipid bilayers or in molecular aggregates such as micelles.

Micelles and lipid bilayers can exert a dramatic influence on the stereochemical aspects of radical pair reactions. Thus reactions that occur with nearly complete loss of stereochemical configuration in isotropic media exhibit significant retention of stereochemical configuration if carried out in micelles or lipid bilayers. The highest diastereoselectivity yet observed for radical pair reactions carried out in micelles or lipid bilayers is over 70%. These observations suggest that radical pair dynamics in molecular aggregates are quite different than in isotropic media and require that the stereochemical tests for radical reactions frequently used as a tool for reaction mechanism be modified. *The rule that a radical pair mechanism requires loss of stereochemical configuration in the pair coupling product is invalid.*

The case of cytochrome P-450 is a notable example. For many years, the radical pair mechanism proposed for this enzymatic conversion was questioned since the reaction-catalyzed, oxygen insertion into a C–H bond was known to occur with high diastereoselectivity in the enzyme-catalyzed reaction. The enzyme has a hydrophobic binding site and the enzyme–radical pair is thus held together by hydrophobic forces. It is, perhaps, not surprising that this radical pair intermediate proceeds to give products with high diastereoselectivity. Similar diastereoselectivities are observed in the reactions of the diazene **39** in molecular aggregates and the hydrophobic effect must be responsible to some extent for the retention of configuration in this system.

Another interesting development deriving from the study of diazene **39** is the observation that molecular aggregates formed from diastereomers may be dramatically different. Diastereoselectivity for decomposition of diazenes in micelles of *meso*-**39** is low while diastereoselectivity for diazene decomposition in (±)-**39** micelles is much higher.

The observation that diastereomeric amphiphiles may form dramatically different aggregates has led us to investigate equilibrium rather than kinetic processes of such aggregates (61). The radical pair studies all involve kinetically controlled products and we have begun a study of substrates analogous to diazene **39** that have a mechanism of equilibration available. With this in mind, we have prepared ketones such as **44** and have studied the equilibration of these ketones in aqueous base (44). Equilibrium is attained for **44** in 1 *M* KOH at 60°C after 200 h and equilibrium mixtures favoring the meso diastereomer by as much as 8/1 : meso/± have been observed. Equilibration of the dimethyl ester of the ketone in organic solvents at 60°C leads to a 50 : 50 mixture of the diastereomers. It is thus clear that the stereochemical conse-



44, meso and ±

quences of equilibrium as well as kinetic processes may be altered by molecular aggregates such as micelles. We are just beginning to investigate these equilibrium processes, but it appears that the aggregates will have as significant impact on these processes as was observed for radical pair coupling phenomena.

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Enantioselective Synthesis of Organic Compounds with Optically Active Transition Metal Catalysts in Substoichiometric Quantities

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ABBREVIATIONS

Diop	[(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]-bis[diphenylphosphine]
Dipamp	1,2-Ethanediylbis[(2-methoxyphenyl)phenylphosphine]
Prophos	(1-Methyl-1,2-ethanediyl)bis[diphenylphosphine]

Chiraphos	(1,2-Dimethyl-1,2-ethanediyl)bis[diphenylphosphine]
Norphos	Bicyclo[2,2,1]hept-5-ene-2,3-diylbis[diphenylphosphine]
BPPM	4-(Diphenylphosphino)-2-[(diphenylphosphino)methyl]-1-pyrrolidinecarboxylic acid-1,1-dimethylethyl-ester
BPPFA	1-[1-(Dimethylamino)ethyl]-1′,2-bis(diphenylphosphino)-ferrocene
Binap	[1,1′-Binaphthalene]-2,2′-diylbis[diphenylphosphine]
TA	Tartaric acid
TA–NaBr–MRNi	Tartaric acid–NaBr–modified Raney nickel
cod	1,5-Cyclooctadiene
nbd	Norbornadiene

I. INTRODUCTION

The first examples of heterogeneous and homogeneous enantioselective catalysis of organic reactions with transition metal systems were reported in 1956 and 1966, respectively (1, 2), not taking into account the extremely low optical inductions obtained earlier with nickel catalysts deposited on dextro or levo quartz (3). The results have been summarized in many reviews, the most recent of which are Bosnich's book *Asymmetric Catalysis* (4) and an entire volume (Volume 5, *Chiral Catalysis*) of Morrison's series *Asymmetric Synthesis* (5). There are other comprehensive reviews of recent date (6–8) covering the whole field, one of which appeared in this series in 1981 (9).

In this situation the choice of a strategy for a new review on enantioselective synthesis with transition metal catalysts was to (i) concentrate mainly on the value of enantioselective catalysis for organic synthesis and (ii) not only present highlights but also a quantitative collection of data. To this end a thorough search of the *Chemical Abstracts Selects* series *Catalysis* (*Organic Reactions*) was carried out. All the references in the 72 *CA Selects* issues between January 1984 and October 1986 were examined, excluding patents. Hence this account covers the literature that appeared after publication of the two books on enantioselective catalysis (4, 5) mentioned before. This complete survey of the three-year period 1984–1986, inclusive, should describe the present status of the field both with respect to routine applications of established procedures and with respect to trends for future developments. A number of recent reviews covering special aspects of the field are available (10–34).

In this chapter only enantioselective syntheses catalyzed by optically active transition metal catalysts are included and only systems that use substoichiometric quantities of optically active catalysts are considered. Such systems are of economic importance because their application results in a multiplication of the chiral information contained in the catalyst, and in principle large amounts of optically active products should be accessible from small amounts of optically active catalysts. This aspect demonstrates the superiority of systems for which substoichiometric quantities of an optically active catalyst are sufficient, compared with systems that need stoichiometric amounts of an optically active auxiliary. The enzymes in man, animals, and plants adhere to the same principle in performing the elegant syntheses of all the optically active compounds essential for life. With simple, robust, and efficient catalysts, for example, the transition metal systems discussed here, chemists enter into competition with nature.

In the following there is a short paragraph on the optically active catalysts. Then the reaction types are discussed to which enantioselective catalysis has been applied. Tables 2 and 3 are the heart of the chapter, comprising all the optically active ligands used to modify the transition metal catalysts and all the optically active organic compounds prepared by enantioselective catalysis in the past three years.

II. TRANSITION METAL CATALYSTS FOR ENANTIOSELECTIVE ORGANIC REACTIONS

A. The Origin of the Optical Activity in the Products

The chiral information in the organic products prepared by enantioselective catalysis derives from the optically active ligands bound to the transition metal. In the first studies of heterogeneous catalysis the protein of silk fibroin was the chiral matrix used in the Pd-catalyzed hydrogenation of prochiral keto groups (1). Homogeneous catalysis started with copper complexes of salicyl aldimine ligands, prepared from optically active primary amines, in the cyclopropanation of olefins with ethyl diazoacetate (2). Then, optically active phosphines took over because of their steric and electronic variability, although other ligand types continued to play a modest role in enantioselective catalysis. The monodentate Horner phosphines PPhPrMe, chiral at the P atom, where the first optically active phosphine ligands introduced into Rh-catalyzed enantioselective hydrogenation of C=C bonds (35, 36), but soon bidentate phosphines became the most important ligands. There is a recent extensive compilation and classification of the optically active ligands used in enantioselective catalysis (37, 38).

Usually, the ligands used in enantioselective catalyses are bidentate, because for a bound chelate ligand the number of possible conformations is reduced compared with two bound unidentate ligands—an effect beneficial for the optical induction on product formation (4, 7). Though progress and success in the field of enantioselective catalysis is still empirical, there are a number of models explaining the transmission of the chiral information in the catalyst from the ligand to the newly forming asymmetric centers of the product, thus correlating ligand configuration and product configuration, for example, in enantioselective hydrogenation (4, 7, 11, 39–44).

B. The "Name" Ligands of Table 1 and the Ligands 1–329 of Table 2

For the 12 ligands of Table 1 there are accepted acronyms which will be used throughout the chapter because they are more informative than the boldface numbers characterizing all the other ligands. The eight most frequently used diphosphines are shown at the beginning of Table 1, arranged according to increasing C, H content in the molecular formula. Except Dipamp, which contains chiral P atoms, in all the other bisphosphines PPh_2 groups are attached to chiral backbones by P–C bonds. The syntheses of the first seven diphosphines are well-established procedures (38); the synthesis of Binap, a fully arylated diphosphine, has been reported recently (45–47). A new chromatographic resolution of Dipamp has appeared in outline form (48). All these diphosphines are air-stable solids, most of which are commercially available. Doubtless, the champion is Diop, which has been used in more than a third of all the studies dealing with enantioselective catalysis in the last three years.

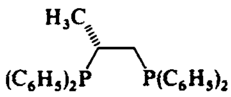
After the monophosphine NMDPP, tartaric acid (used to modify heterogeneous catalysts) (10, 15, 25, 30), diethyl tartrate (used in Sharpless' epoxidation of allyl alcohols (4, 49–56) and Kagan's oxidation of sulfides (57, 58)), and the nitrogen ligand Pythia (used for the hydrosilylation of prochiral ketones) (11, 34, 59, 60) are included at the end of Table 1. These ligands are commercially available or readily accessible, for example, Pythia is prepared in a one-step condensation from 2-acetylpyridine and (*S*)-methyl cysteinate (60). In contrast, the optically active phosphines are rather expensive ligands, because their syntheses usually comprise many steps. However, to make catalysts less expensive may not only involve the ligands but also the metals. So the noble metals Rh, Pd, and Pt can be replaced by inexpensive 3*d* metals, such as Fe, Co, Ni, and Cu (34).

In the last three years 329 optically active ligands, arranged in Table 2 in Section IV according to their formulas, have been used in enantioselective catalysis. Many of them are phosphorus compounds which on coordination form M–P bonds, the most promising being Pyrphos (61–63), Dpcp (64), and BDPP (65–67).

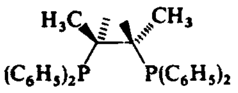
In addition to ligands having only P–C bonds, a large number of new phosphorus ligands that contain P–N and P–O bonds has been reported. They are usually prepared by phosphinylation of optically active NH and

Table 1

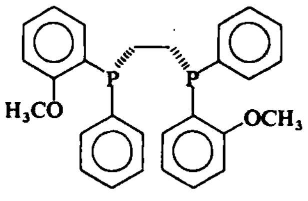
Frequently Used Optically Active Ligands with Their Generally Accepted Acronyms


H_3C
$(C_6H_5)_2P$
$P(C_6H_5)_2$

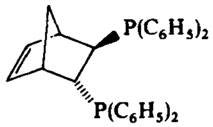
(*R*)-(+)-Prophos
171


H_3C
CH_3
$(C_6H_5)_2P$
$P(C_6H_5)_2$

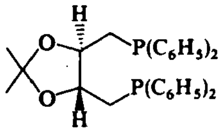
(2*S*,3*S*)-(−)-Chiraphos
178


P
P
H_3CO
OCH_3

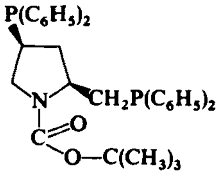
(*R*,*R*)-(−)-Dipamp
177


$P(C_6H_5)_2$
$P(C_6H_5)_2$

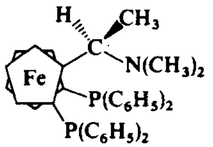
(*R*,*R*)-(−)-Norphos
213


H
O
O
$P(C_6H_5)_2$
$P(C_6H_5)_2$
H

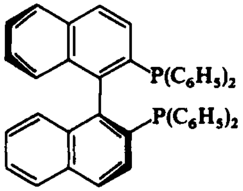
(*R*,*R*)-(−)-Diop
216


$P(C_6H_5)_2$
N
$CH_2P(C_6H_5)_2$
C
O
$O—C(CH_3)_3$

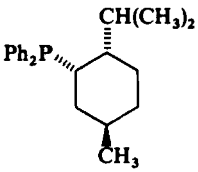
(2*S*,4*S*)-(−)-BPPM
245


H
CH_3
C
$N(CH_3)_2$
Fe
$P(C_6H_5)_2$
$P(C_6H_5)_2$

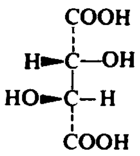
(R_C,S_{F_C})-(−)-BPPFA
274


$P(C_6H_5)_2$
$P(C_6H_5)_2$

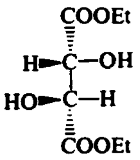
(*S*)-(−)-Binap
293


$CH(CH_3)_2$
Ph_2P
CH_3

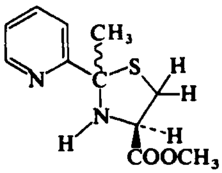
(1*S*,2*S*,5*R*)-(+)-NMDPP
145


COOH
H
C
OH
HO
C
H
COOH

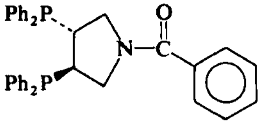
(*R*,*R*)-(+)-TA
3


COOEt
H
C
OH
HO
C
H
COOEt

(*R*,*R*)-(+)-DET
21

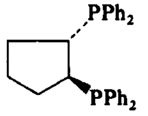

N
CH_3
C
S
H
H
N
H
H
$COOCH_3$

(4*R*)-(+)-Pythia
39



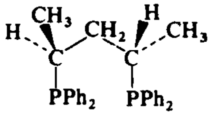
(*R*,*R*)-(+)-Pyrphos

248



(*S*,*S*)-(−)-Dpcp

186



(*S*,*S*)-(−)-BDPP

193

OH compounds, such as amino alcohols or carbohydrates. However, these compounds tend to suffer P–N and P–O bond cleavage, especially in alcoholic solvents, which are frequently necessary (e.g., for hydrogenation reactions). Increasingly, however, there are ligands that bind to the metal atom by nitrogen atoms, sometimes also by sulfur or oxygen atoms.

C. *In Situ* Catalysts—Isolated Catalysts

Frequently, the catalyst for an enantioselective synthesis is prepared *in situ* from a so-called procatalyst and cocatalyst. The procatalyst usually is a stable commercially available compound, for example, $Cu(OAc)_2$, $[Rh(cod)Cl]_2$ (cod = 1,5-cyclooctadiene), $[Rh(nbd)_2]BF_4$ (nbd = norbornadiene), $Pd(dba)_2$ (dba = dibenzylideneacetone), and the cocatalyst is an optically active ligand. In solution procatalyst and cocatalyst combine to give the active catalyst—a simple recipe for routine application. Such *in situ* catalysts can be prepared within minutes before a reaction is carried out. Another argument in favor of *in situ* catalysts is the possibility of changing the metal-to-ligand ratio. Hence a ligand excess may increase the optical yield, for example, by suppressing an achiral reaction channel.

Sometimes isolated compounds are used as catalysts in enantioselective synthesis. Occasionally they will give better chemical or optical yields and invariably they will be more suitable to mechanistic studies than *in situ* catalysts. However, the necessity of synthesizing a catalyst in an extra step prior to the actual catalysis will be an obstacle to routine application.

D. Homogeneous Catalysts—Heterogeneous Catalysts

Homogeneous catalysts are said to be more selective than heterogeneous catalysts, especially with respect to optical induction. According to a general argument, an ideal homogeneous catalyst should be present in solution only in the form of one catalytically active species, which could be adapted to a specific substrate (e.g., by tailoring the optically active ligand). A heterogeneous catalyst is more likely to contain different catalytically active sites on its surface. Each of these sites would have its own selectivity, and a low overall selectivity would result. An advantage of a heterogeneous catalyst is its easy separation from the reaction mixture and its potential reuse, whereas the recycling of a homogeneous catalyst with respect to the metal and even more with respect to the ligand is a problem.

Heterogeneous catalysts can be prepared in different ways. The catalytically active transition metal centers, deposited on a support, usually are chirally modified by treatment with a solution of an optically active compound (e.g., amino acids, hydroxy acids, amines, and amino alcohols) with (*R*, *R*)-(+)-tartaric acid (TA) at the head of the optically active modifiers. Reaction conditions as well as pre- and post-treatment decisively influence the enantioselectivity, as substantiated by the recent reviews (10, 15, 25, 30) written by the most innovative authors in the field.

The most developed system to date is TA–NaBr–MRNi (tartaric acid–NaBr–modified Raney nickel). Raney nickel modified with (*R*, *R*)-(+)-tartaric acid improves its enantioselectivity on treatment with NaBr (68). Additional modification with 1-methylpropylamine or pyridine gives a durable heterogeneous system which can be repeatedly used for the 90% e.e. hydrogenation of methyl acetoacetate without decrease in enantioselectivity (69). Of all the other reported heterogeneous catalysts, only Orito's system, platinum on a support, modified with quinine or cinchonidine, in the hydrogenation of α-keto esters, somewhat matches the TA–NaBr–MRNi catalyst (26).

Heterogeneous catalysts can also be prepared by immobilizing transition metal compounds such that they do not dissolve during catalysis. An example is the impregnation of charcoal, pretreated with NaOAc, with soluble Rh/Diop catalysts that achieve the same e.e. as the corresponding homogeneous catalysts (70). Also, transition metal salts with optically active anions are heterogeneous catalysts, if they are insoluble in the reaction medium. Thus, copper tartrate has been used in the enantioselective cyclopropanation (71) and the Lewis acid zinc tartrate in the enantioselective ring opening of epoxides with thiols (72).

The link between homogeneous and heterogeneous catalysts is the so-called heterogenized homogeneous catalysts. In their preparation, a ligand to which a metal fragment can coordinate is covalently bonded to a surface by some suitable functionality. If additionally a spacer between surface and catalytic site is introduced, such a heterogeneous catalyst closely resembles its homogeneous counterpart. In principle, a heterogenized homogeneous catalyst should combine the advantages of homogeneous and heterogeneous catalysts. A problem associated with heterogenized homogeneous catalysts is their loss of activity and enantioselectivity because of metal leaching (73, 74).

A recent example of a heterogenized homogeneous catalyst is the ligand

Pyrphos attached to a silica surface via dicarboxylic acid spacers, which in the hydrogenation of methyl (*Z*)-α-*N*-acetamidocinnamate is reported to give 100% e.e. (61, 62). The principle of double stereoselection was used with a rhodium catalyst attached to a Diop-containing polymer with additional pending alcohol groups. In going from racemic to (*S*)-configurated alcohol groups, an increase of the optical yield in the hydrogenation of (*Z*)-α-*N*-acetamidocinnamic acid by 8% was achieved (75, 76). The highest optical induction in a hydroformylation reaction with a heterogeneous catalyst was obtained with $PtCl_2/SnCl_2$ on a BPPM-polymer (77). The product hydratropaldehyde had an e.e. of 70%. In the cyclopropanation of styrene by 2-diazodimedone with an immobilized Cu β-diketonate 100% e.e. has been reported (78).

III. REACTION TYPES SUBJECT TO ENANTIOSELECTIVE CATALYSIS

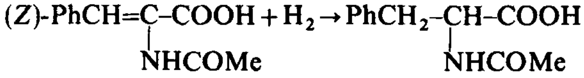
For each of the following reactions the general type is described first, followed by typical examples. When appropriate, there are remarks on the history, importance, and industrial application of the reaction type. Then the scope of substrates and catalysts is discussed with emphasis on papers published during the last three years. Mechanisms, which are extensively covered in refs. 4 and 5, are mentioned only briefly unless there are new aspects.

A. Hydrogenation of Unsaturated Compounds with Molecular Hydrogen

In the vast majority of optically active compounds a hydrogen atom is attached to the asymmetric carbon atom. These hydrogen atoms can be introduced into appropriate unsaturated precursors in hydrogenation reactions with gaseous hydrogen. The hydrogenation of C=C, C=N, and C=O bonds in olefins, imines, and ketones with prochiral centers leads to saturated derivatives containing nitrogen and oxygen functionalities directly bonded to the chiral center. Thus hydrogenation is a reaction of fundamental importance for the synthesis of a variety of optically active compounds.

In 1968 the enantioselective hydrogenation of prochiral C=C bonds with Wilkinson-type Rh complexes (79) of monodentate phosphines, chiral at the P atom, started simultaneously in the groups of Horner and Knowles (35, 36). Major breakthroughs were (i) the synthesis of the diphosphine Diop from tartaric acid, which increasingly called attention to chelate phosphines (80, 81), and (ii) the introduction of dehydroamino acids as substrates, such as (*Z*)-α-*N*-acetamidocinnamic acid (eq. [1]), which could be hydrogenated to amino acids with high e.e.'s (80, 82), culminating in the industrial synthesis of L-dopa, a drug used to treat Parkinson's disease (31). These spectacular achievements have been reviewed frequently; reviews that appeared after 1980 are refs. 4, 6–9, 12, 14, 17, 21–23, 31, 34, 43, 83–97, and 325.

Dehydroamino acids are the most frequently used substrates in enantioselective catalysis, especially (*Z*)-α-*N*-acetamidocinnamic acid (eq. [1]) and its methyl ester. These as well as α-*N*-acetamidoacrylic acid and its methyl ester have become the standard substrates used in the report period in dozens of papers (45, 98–138, 316).



$$(Z)\text{-PhCH=}\underset{\text{NHCOMe}}{\underset{|}{\text{C}}}\text{-COOH} + \text{H}_2 \rightarrow \text{PhCH}_2\text{-}\underset{\text{NHCOMe}}{\underset{|}{\text{CH}}}\text{-COOH} \qquad [1]$$

These substrates were applied to test new ligands typically incorporated in rhodium catalysts (98–131, 316), new water soluble catalysts (63, 132–135), new homogeneous catalysts based on 3*d* metals such as cobalt, and nickel (136–138), new heterogeneous catalysts containing rhodium complexes of polymer-bound phosphine ligands (61, 62, 74, 75), or rhodium complexes impregnated on pretreated charcoal (70).

The reaction mechanism of these enantioselective hydrogenations has been elucidated by Halpern (25, 96, 97, 139–141). For dehydroamino acid substrates, such as methyl (*Z*)-α-acetamidocinnamate, bidentate coordination via the C=C bond and the oxygen atom of the *N*-acetyl group has been established. The reaction follows the "olefin route," which means that coordination of the olefin precedes the oxidative addition of the H_2 molecule. Surprisingly, it was found that the prevailing configuration of the product comes from the minor diastereomer of a pair of equilibrating diastereomers. Consequently, the minor diastereomer must be more reactive than the major diastereomer in the rate-determining reaction with hydrogen. This has been supported by a study of the corresponding iridium compounds, which are more stable than their rhodium analogs (143), and by model considerations (144). The mechanism of enantioselective hydrogenation contrasts with that of the palladium-catalyzed allylic alkylation, discussed later, in which there is also an equilibrium of two diastereomers, but the major product enantiomer originates from the major diastereomer.

Most of the optically active phosphines used in enantioselective hydrogenation are chelating diphosphines containing two PPh_2 groups whose chirality is located on the carbon skeleton between them (37, 38). Thus, in a chelate complex, the inducing chirality is 4–5 Å away from the metal coordination site, where the prochiral groups are converted into the new chiral centers of the optically active product. It is well established that the chiral information is transmitted within the catalyst by the puckering of the chelate rings. In the five-membered chelate rings of Prophos, Chiraphos, Dipamp, or Norphos complexes, the alkyl substituents at the asymmetric carbon atoms tend to occupy the sterically less hindered equatorial positions and the hydrogen substituents adopt the axial positions. This reinforces the puckering of the chelate ring into a chiral conformation which in turn differentiates the two phenyl substituents at each phosphorus atom into equatorial and axial. It is the chiral array of the two phenyl "ears" at the phosphorus atoms which hands over the chiral information to the prochiral groups or faces in the substrates binding at the adjacent positions (4, 7, 34, 39–43). This model allows a correlation of the product configuration with the inducing configurations in the ligands.

The substituent in the β-position of the dehydroamino acid can be either an aryl or an alkyl group without appreciable decrease in the optical induction of the hydrogenation (95, 118, 125, 131, 145). The substituent can be in the (*E*)- or (*Z*)-position (7, 95) or in both positions (95, 146, 147). In the report period, the enantioselective dehydroamino acid hydrogenation was applied to the synthesis of chlamydocin (148) and cyclopeptide alkaloids (149). The dehydroamino acid moiety could also be made part of a tetrahydroisoquinoline system. The hydrogenation with Ru(Binap) (acetate)$_2$ as a catalyst afforded 1-substituted tetrahydroisoquinolines with optical inductions close to 100%. This represents the most important step in the newly established commercial production of tetrahydropapaverine, laudanosine, norreticuline, and salsolidine (150), which previously had been obtained only with 45% e.e. (146).

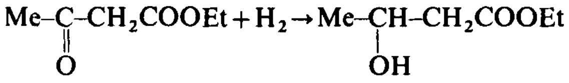
In dehydrodipeptides, the dehydroamino acid moiety can be combined with an optically active amino acid. Double stereoselection (22) is therefore possible on enantioselective hydrogenation (14, 100, 119, 151). There are recent examples in which the asymmetric catalyst modifies the contribution of the amino acid chirality in the substrate only a little (substrate control) (152, 153). However, there are also examples in which the contribution of the catalyst dominates (catalyst control), allowing the transformation of the dehydroamino acid part into a *S* or *R* amino acid component of the dipeptide with high diastereomeric excess (114, 154). These studies have been extended to tripeptides and the synthesis of Enkephalin analogs (154).

Whereas a change of the β-substituents in the dehydroamino acid molecule usually does not decrease the high e.e. in the enantioselective hydrogenation, a change of the acetamido and carboxyl substituents is critical. High e.e.'s on hydrogenation are only obtained when the substituent replacing the acetamido group may chelate to the rhodium atom and when the substituent replacing the carboxyl group is an electron-withdrawing substituent (4, 7, 95).

It has been shown that the enantioselective hydrogenation can be successfully extended from dehydroamino acids to the corresponding dehydrophosphonic acids (155). In going from itaconic acid to α-phenyl cinnamic, α-methyl cinnamic, and tiglic acid, however, hydrogenation with high e.e. becomes increasingly difficult (116, 117, 156). When the new system incorporating modified palladium/methylviologen and enzymes such as enoate reductase is used, enantioselectivities close to 100% e.e. are obtained (157). In geraniol and nerol, the C=C bond of the allylic alcohol unit was hydrogenated with Rh/Binap catalysts with an e.e. up to 66% (158). The OH-directed enantioselective hydrogenation was applied to homoallylic alcohols (159, 160). α,β-Unsaturated ketones were converted into saturated ketones with low e.e. using phosphine derivatives of cobalt carbonyl (161). Enantioselective hydrogenation is most difficult for olefins containing nonfunctionalized double bonds (65, 162, 163). Recently, up to 54% e.e. has been achieved in the hydrogenation of α-ethylstyrene with Rh/BDPP catalysts (65).

For the hydrogenation of ketones, the rhodium catalysts are less efficient than for olefin hydrogenation, both with respect to reaction rate and enantioselectivity (4, 7, 12, 21, 115, 334). Improvements in the catalysts include the addition of amines (164) or the use of optically active phosphines with alkyl substituents at phosphorus instead of phenyl (4), for example, the cyclohexyl derivatives of Diop and BPPM (165, 166). Acetophenone has been hydrogenated to 1-phenylethanol (82% e.e.) with a rhodium catalyst of BDPP (65). Usually, nonfunctionalized ketones give lower e.e. (167, 168) than do functionalized ketones (166, 169, 170) such as α-ketopantolactone which is hydrogenated to 84% e.e. with a $[Rh(cod)Cl]_2$/BPPM catalyst (169) according to a procedure in *Organic Synthesis.* A new reaction type is the hydrogenation of cyclic anhydrides, in which the reduction of one of the two carbonyl groups gives lactones with an e.e. up to 40% (115, 171, 172).

Whereas the catalysts for ketone reduction cited above are homogeneous systems, the enantioselective hydrogenation of carbonyl groups is an area of traditional success for heterogeneous catalysts. In the report period, the system TA–NaBr–MRNi has been developed into a durable catalyst by amine modification (69). This catalyst appears to be the best for repeated use in reactions such as the hydrogenation of acetoacetate to 3-hydroxybutanoate esters (eq. [2]), this being the model reaction for testing heterogeneous catalysts (173–184).



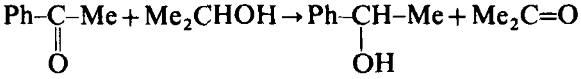
$$\mathrm{Me{-}\underset{\underset{O}{\|}}{C}{-}CH_2COOEt + H_2 \rightarrow Me{-}\underset{\underset{OH}{|}}{C}H{-}CH_2COOEt} \qquad [2]$$

Recently, the hydrogenation of a β-ketoester with tartaric acid modified Raney nickel was used as an enantioselective step in the synthesis of the sex attractant of pine sawflies (185). The reduction of a variety of methyl ketones was achieved with the TA–NaBr–MRNi system (186), the presence of carboxylic acids being indispensable for achievement of high e.e.'s.

The enantioselective hydrogenation of the C=N bond in ketimines, which gives secondary amines, is a somewhat neglected area. In the period under review, the imine of acetophenone and benzylamine was reduced with 73% e.e. using a Rh/BDPP catalyst (65) and with more than 60% e.e. using Rh/phosphine catalysts in the presence of halide ligands (187).

B. Transfer Hydrogenation

In a transfer hydrogenation, hydrogen donors, for example, isopropyl alcohol or formic acid, are used instead of molecular hydrogen. Two hydrogen atoms are transferred from the hydrogen donor to an unsaturated substrate. A typical transfer hydrogenation is the reduction of acetophenone with isopropyl alcohol (eq. [3]).



$$\mathrm{Ph{-}}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}Me} + \mathrm{Me_2CHOH} \rightarrow \mathrm{Ph{-}}\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}\mathrm{H{-}Me} + \mathrm{Me_2C{=}O} \qquad [3]$$

The reaction type is known as Meerwein–Ponndorf–Verley reduction if the isopropyl alcohol–aluminium isopropoxide system is used (188). In recent years, transition metal catalysts were found which catalyze transfer hydrogenations much more effectively than $Al(i\text{-}OC_3H_7)_3$. Homogeneous and heterogeneous variants of the transfer hydrogenation have been reviewed (189, 190).

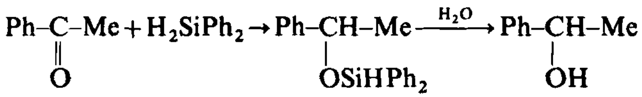
With rhodium and iridium catalysts containing optically active *P*- or *N*-ligands, secondary alcohols were obtained from ketones with optical inductions in the middle range (66, 191–194). Sometimes the activation of the transfer hydrogenation catalysts is so critical that an inversion of the sign of optical induction is observed under different reaction conditions (194). The reduction of the α-keto group in methyl phenylglyoxylate by NADH to give methyl mandelate is catalyzed by the chiral shift reagents $Eu(tfc)_3$ and $Eu(hfc)_3$ with up to 55% e.e. (195).

The hydrogen from hydrogen donors can also be transferred to C=C bonds. Thus (*E*)-α-methylcrotonic acid was hydrogenated by 1-phenylethanol using $Ru_2Cl_4(Diop)_3$ with 26.4% e.e. (196). Recently, formic acid/Na formate was used for a transfer hydrogenation of the C=C bond in acetamidocinnamic acid and other dehydroamino acids. For some systems higher e.e.'s than for the hydrogenation with gaseous hydrogen were obtained (197).

C. Hydrosilylation

The Si–H bond in silanes can be activated much more readily than the H–H bond in molecular hydrogen. Hence a large number of transition metal compounds catalyzes the Si–H addition to C=C, C=N, and C=O bonds.

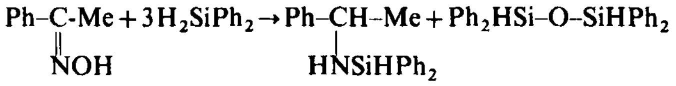
The most important of these addition reactions is the hydrosilylation of carbonyl compounds. Because of its oxophilicity, the silicon fragment regiospecifically adds to the oxygen atom of the C=O bond and the hydrogen atom is delivered to the carbon atom. As O–Si bonds are easily hydrolyzed, the hydrosilylation of a ketone followed by hydrolysis is a reduction to the corresponding alcohol. The enantioselective variant of this reaction has been reviewed frequently (4, 6–9, 11, 14, 21, 27, 198–203). The first enantioselective hydrosilylation of acetophenone was described in 1972 (204). Its hydrosilylation with diphenylsilane and the subsequent hydrolysis to give 1-phenylethanol (eq. [4]) is a frequently used model reaction.



$$\mathrm{Ph{-}\underset{\underset{O}{\|}}{C}{-}Me + H_2SiPh_2 \rightarrow Ph{-}\underset{\underset{OSiHPh_2}{|}}{CH}{-}Me \xrightarrow{H_2O} Ph{-}\underset{\underset{OH}{|}}{CH}{-}Me} \qquad [4]$$

The product configuration and the optical yield strongly depend on the substituents at the carbonyl group and the silicon atom. Special success has been reported for the application of the silane (1-Np)PhSiH$_2$ and for the reduction of α-keto esters (4, 6–9, 14, 154, 198–203). Platinum, iridium and especially rhodium compounds containing chelating diphosphines usually are used as catalysts (122, 124, 205–208). Recently, however, it has been shown that it is possible to replace rhodium and platinum compounds by copper compounds (209) and phosphine ligands by nitrogen ligands, such as pyridine imines (59, 210) and pyridine thiazolidines (59, 60). Both substitutions point to possible improvements in enantioselective catalysis with transition metal compounds, viz., the use of cheap 3*d* metals instead of noble metals and of readily available nitrogen ligands, accessible in one-step condensations, instead of expensive phosphorus ligands, accessible only in many-step syntheses. Furthermore, the pyridine thiazolidine ligands give much higher optical inductions in the hydrosilylation of ketones than the diphosphines used to date (60). The highest reported e.e. with a [Rh(cod)Cl]$_2$/pyridine thiazolidine catalyst for the system acetophenone/diphenylsilane is 97.6% e.e. (60).

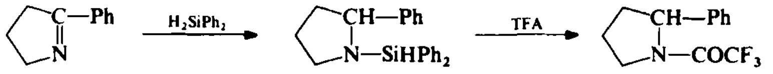
Oximes obtained from ketones can be reduced with diphenylsilane using a catalyst formed *in situ* [Rh(cod)Cl]$_2$/(–)-Diop (211, 212). Three moles of diphenylsilane are consumed in this reaction, two of which end up in the disiloxane Ph$_2$HSi–O–SiHPh$_2$ and the third in the silylamine (eq. [5]), which on hydrolysis gives the corresponding primary amine.



$$\mathrm{Ph{-}\underset{\underset{NOH}{\Vert}}{C}{-}Me + 3H_2SiPh_2 \rightarrow Ph{-}\underset{\underset{HNSiHPh_2}{|}}{CH}{-}Me + Ph_2HSi{-}O{-}SiHPh_2} \qquad [5]$$

In the study of a series of ketoximes, chemical yields between 30 and 60% and optical inductions up to 32% e.e. were obtained (212). The reaction seems to take place via an imine intermediate since the corresponding imines, which can be isolated if they contain *o*-substituted aryl groups, give the same optical inductions as the oximes (212). This new reaction allows the transformation of a prochiral ketone into optically active primary amines via enantioselective catalytic hydrosilylation of the oxime, which usually is readily accessible.

For the enantioselective hydrosilylation of imines, analogous to that of ketones, there are only scattered examples. The hydrosilylation products of imines can be hydrolyzed to give the corresponding secondary amines (198) or derivatized with trifluoroacetic anhydride to give trifluoroacetamides (eq. [6]).



[6]

A [Rh(cod)Cl]$_2$/Diop catalyst gave 62% e.e. in this reaction (213). With a 3-pyridyl substituent instead of phenyl, the nicotine derivative was obtained with more than 60% e.e. (213).

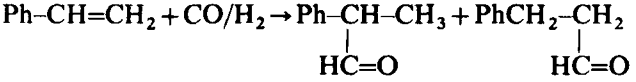
The course of the hydrosilylation of α,β-unsaturated carbonyl compounds strongly depends on the type of silane used. Whereas monohydrosilanes tend to give 1,4 addition, dihydrosilanes and trihydrosilanes favor 1,2 addition to the carbonyl group (214). On hydrolysis, the 1,4 addition products are converted to saturated carbonyl compounds and the 1,2 addition products to allylic alcohols. Both types of reactions have been carried out enantioselectively (4, 7, 198).

In the addition of a Si–H bond to an unsymmetrical olefin, regioisomers are possible. Proper choice of the silane, however, allows control of the direction of addition and a number of optically active alkyl–silicon derivatives has been prepared by enantioselective hydrosilylation of olefins (4, 198). This reaction is of some importance since the cleavage of the alkyl–silicon bond in optically active silicon compounds leads to alcohols or alkyl halides without loss of optical activity. Allylsilanes are formed in the hydrosilylation of conjugated dienes (4, 198). The reaction has been applied recently to open-chain and cyclic dienes (215, 216).

D. Hydroformylation and Hydrocarboxylation

The hydroformylation of olefins has been an industrially important reaction for many decades. It is usually carried out with a 1 : 1 mixture of CO and H_2. In this reaction, a hydrogen atom and a formyl group are added to a C=C bond giving rise to two regioisomers in the case of unsymmetrical olefins. Depending on the structure of the olefin, the formation of the new C–H and C–C bonds may create new chiral centers. There are examples of both types of enantioselective catalyses (4, 6–9, 28, 86, 198, 217–219, 327, 337). A detailed recent review is available (220).

In the most intensely studied hydroformylation, that of styrene (eq. [7]), only the branched chain product is chiral.

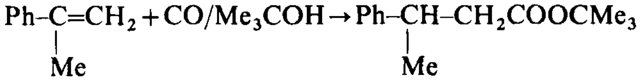


$$\mathrm{Ph{-}CH{=}CH_2 + CO/H_2 \rightarrow Ph{-}\underset{HC=O}{\underset{|}{CH}}{-}CH_3 + PhCH_2{-}\underset{HC=O}{\underset{|}{CH_2}}} \qquad [7]$$

The first enantioselective hydroformylation of styrene was described in 1972 (221). Now optical yields up to 85% e.e. are attainable with styrene (4, 103), whereas optical inductions of other olefins are much lower, especially for functionalized olefins (4, 198). Usually, rhodium and platinum, the latter in combination with $SnCl_2$, are employed as catalysts. Problems associated with the enantioselective hydroformylation are the low yield of the chiral product as well as the accompanying hydrogenation and isomerization of the olefin. A quadrant rule has been developed to predict the direction of optical induction, to which most of the systems adhere (219, 220, 224).

Recently, the hydroformylation of the butene isomers has been reinvestigated (222). For 1-butene the highest induction of 47% e.e. for a purely aliphatic olefin was obtained at 60°C, because at this low temperature the side reactions were slow. At higher temperatures, fast isomerization takes place, a process responsible for the discrepancies in the literature (222). The study has implications for the mechanism of the hydroformylation. The regiochemistry and the optical induction in the hydroformylation with (Diop)Pt($SnCl_3$)Cl catalysts are determined while or before the alkyl–platinum intermediate is formed and not afterward, as had been assumed (4, 7, 198, 219, 220, 223). It is in the hydroformylation reaction that many of the heterogeneous catalysts were tested. Usually they give rise to enantioselectivities comparable to those of the corresponding homogeneous systems (19, 28, 76, 86, 327).

A reaction related to hydroformylation is hydrocarboxylation, also called hydroesterification. In this reaction an olefin is converted to a carboxylic acid ester on treatment with CO in an alcohol. To some extent, the regioselectivity can be controlled by the proper choice of the alcohol (4, 198, 219). The first enantioselective hydrocarboxylation was reported in 1973 (225). The hydroesterification of α-methylstyrene is shown in eq. [8].

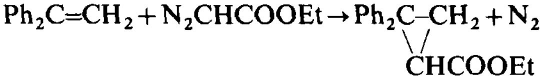


$$\underset{\displaystyle Me}{\mathrm{Ph{-}\underset{|}{C}{=}CH_2}} + \mathrm{CO/Me_3COH} \rightarrow \mathrm{Ph{-}\underset{\displaystyle \overset{|}{Me}}{CH}{-}CH_2COOCMe_3} \qquad [8]$$

In this reaction up to 69% e.e. was obtained with $PdCl_2$/Diphol catalysts (226, 227). Optical yields are allyl–phthalimides were much lower (228). As in hydroformylation, enantioselection seems to occur during or before the formation of the platinum–alkyl species. Models allow a prediction of the preferred configuration in enantioselective reactions.

E. Cyclopropanation

Treatment of an olefin with a diazo compound, such as a diazoacetate, gives rise to a cyclopropane with elimination of N_2 when catalyzed with Cu, Co, or Rh catalysts, as shown in eq. [9] for 1,1-diphenylethylene (208, 229).



$$\mathrm{Ph_2C{=}CH_2 + N_2CHCOOEt \rightarrow Ph_2C{-}CH_2 + N_2} \quad \text{with } \mathrm{CHCOOEt} \text{ bridging below} \qquad [9]$$

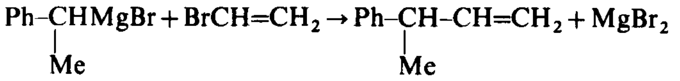
Cyclopropanes related to chrysanthemic acid are used on a large scale as insecticides (pyrethroids). Their biological activity is strongly dependent on the configuration of the asymmetric carbon atoms in the cyclopropane ring (230). In 1966 a cyclopropanation reaction was the first enantioselective reaction to be carried out with homogeneous catalysis by a transition metal compound (2). Since then, cyclopropanation has become a standard reaction in enantioselective catalysis. The highest optical induction obtained up to now is 95% e.e. (231). Reviews of this reaction are available (4, 6–9, 24, 341).

Recently, new olefins have been added to the list of substrates (78, 232, 233). Virtually complete optical induction has been achieved with heterogeneous immobilized Cu-β-diketonates in the reaction of 2-diazodimedone with styrene (78). Copper tartrate was used in the synthesis of ring B of the steroid skeleton (71). Cyclopropane rings were formed in low chemical and optical yields on treatment of buten-3-al-1 derivatives with Zn/HOAc using Cobalamin as the catalyst (234).

F. Grignard Cross-Coupling

Vinyl halides and aryl halides are relatively unreactive toward Grignard reagents. These reactions, however, can be catalyzed by nickel or palladium complexes. Enantioselective product formation is observed with optically active ligands, ferrocenylphosphines, and β-dimethylamino alkylphosphines being most successful (4, 7, 203, 235–237). Obviously, the dimethylamino group, present in both types of ligands, participates in the transition state of the transmetallation, which transfers the alkyl group from the Grignard to the transition metal in the enantioselective step. Recently, macrocyclic ligands with sulfide and amine binding sites have been successfully applied to the Grignard cross-coupling reaction (18, 238, 239).

The reaction of the 1-phenylethyl Grignard reagent with vinyl bromide (eq. [10]) continues to be a frequently studied model system (238–241).



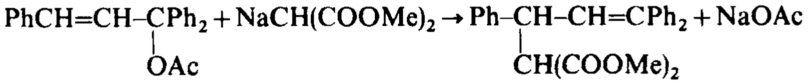
$$\underset{\displaystyle Me}{\text{Ph--}\underset{|}{\text{C}}\text{HMgBr}} + \text{BrCH=CH}_2 \rightarrow \underset{\displaystyle Me}{\text{Ph--}\underset{|}{\text{C}}\text{H--CH=CH}_2} + \text{MgBr}_2 \qquad [10]$$

In 1973 this reaction was the first enantioselective Grignard cross-coupling to be studied (242, 243). Besides 1-phenylethyl Grignard other secondary alkyl Grignards have been used (244), the most successful of which is α-trimethylsilylbenzyl Grignard (245). Coupling of the latter with vinyl bromide and other alkenyl bromides proceeded with 95% e.e.. The resulting allylsilanes are useful starting materials for further functionalizations (246–248).

The Grignard cross-coupling reaction is fast compared to the racemization of the chiral Grignard reagents during the reaction (4, 237). Sometimes the optical purity and even the configuration of the products alter with a change of the halide in the Grignard or in its coupling partner (244). Organozinc reagents may show higher stereoselectivity than Grignard reagents (249). The coupling of Grignard reagents and organozinc reagents with allyl compounds is dealt with in the next section.

G. Allylic Alkylation

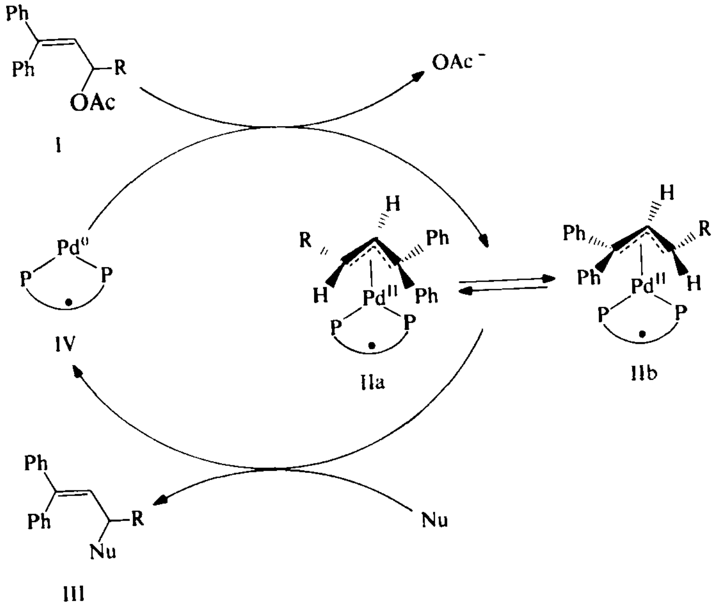
Allylic substrates, usually allylic acetates, can be alkylated by nucleophiles in a palladium- or nickel-catalyzed reaction, involving η^3-allyl intermediates. Depending on the structure of the allylic compounds and the nucleophile, new chiral centers can be formed in both parts of the alkylation product. As (i) chiral or prochiral allylic compounds can be used as starting materials, (ii) the epimerization of the π-allyl intermediates can be fast or slow, and (iii) the nucleophile can attack both at positions 1 or 3 of the allyl intermediate, allylic alkylation subdivides into a number of different types (4, 237, 323, 338). The most highly developed system, reaction of 1,1,3-triphenylprop-2-enyl acetate with sodium dimethylmalonate (eq. [11]), give an optical induction of 86% e.e. (250, 251).



$$\underset{\displaystyle\text{OAc}}{\text{PhCH=CH-CPh}_2} + \text{NaCH(COOMe)}_2 \rightarrow \underset{\displaystyle\text{CH(COOMe)}_2}{\text{Ph-CH-CH=CPh}_2} + \text{NaOAc}$$

[11]

The mechanism of the palladium-catalyzed allylic alkylation with soft nucleophiles was unravelled by Bosnich (4, 237, 250–252). As this elegant study was published in the report period, it is discussed in some detail here (Scheme 1).



Scheme 1

The catalyst, the air-stable complex $[(\eta^3\text{-C}_3\text{H}_5)\text{Pd}((S, S)\text{-Chiraphos})]\text{ClO}_4$, is converted by reaction with the nucleophile into the Pd(O)/Chiraphos species IV which oxidatively adds the substrate I to give the new π-allyl complexes IIa and IIb. The attack of II by the nucleophile regenerates Pd(O)/Chiraphos IV and leads to the substitution product III, which can be isolated or converted into phenylsuccinic acid (R = Ph), a useful chiral synthon (250–252).

In the catalytic cycle shown in Scheme 1, the turnover limiting step, which is simultaneously the enantioselectivity determining step, is the reaction of the π-allyl intermediates IIa and IIb with the nucleophile. This step is slow compared with the oxidative addition of the allylic acetate I to the Pd(O)/Chiraphos complex IV and with the epimerization of the diastereomers IIa and IIb. This means that the final stereochemical outcome is independent of the stereoselectivity of the oxidative addition of the allylic acetate substrates to the Pd(O)/diphosphine catalyst. Furthermore, the results are the same irrespective of whether 1,1,3-triphenylallyl acetate (eq. [11]) or its 1,3,3-isomer is used. The 1,1-diphenyl group in substrate I has proven especially valuable because it facilitates the epimerization of diastereomers IIa and IIb, assuring high optical yields, and it directs the attack of the nucleophile regiospecifically to the less hindered position (250, 251).

The enantiomeric excess of the catalytic allylic alkylation is determined by the relative rates of the attack of the nucleophile at the two diastereomers IIa and IIb. As this step is assumed to be strongly exothermic, the chiral discrimination in the ground state intermediates should be reflected in the corresponding diastereomeric transition states. For reaction II /Scheme 1 it was firmly established that the major enantiomer of the product III originates from the major diastereomer of the equilibrium IIa$\leftrightarrows$IIb. Thus the enantioselective step in the palladium-catalyzed alkylation is under reactant control, whereas the rhodium-catalyzed hydrogenation of dehydroamino acids, mentioned before, is under product control (4, 250, 251).

A detailed labeling study has demonstrated that the formation of the π-allyl complexes II starting from chiral allyl acetates occurs with inversion of configuration in the oxidative addition step and the nucleophile attacks the π-allyl intermediates from the side opposite to the palladium, also leading to inversion (250, 251). Hence the palladium-catalyzed allylation actually is a double inversion (253–255).

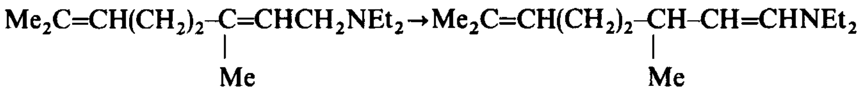
In the report period a series of new studies of palladium-catalyzed enantioselective allylic alkylations with soft nucleophiles has been described (250, 251, 256–261). To overcome the distal relationship between the incoming nucleophile and the inducing metal–ligand moiety, ligands that create chiral pockets were designed based on 1,1-binaphthol. Products having e.e.'s up to 70% were thus obtained (258). Application of new ferrocenylphosphine ligands functionalized with long substituents forced the optical induction up to 92— e.e. (259). In a recent kinetic resolution, palladium-catalysts containing these ferrocenylphosphines were reported to give up to 99% e.e. for the recovered allyl acetate and 98% e.e. for the substitution product (260). A new amino acid synthesis was described in which the anion of the Schiff base, derived from methyl glycinate and benzophenone, was allylated with allyl acetate (261). The resulting 57% e.e. is the highest optical induction observed for an allylation with a nucleophile that contains the prochiral group to be transformed into the new chiral center.

Allylic alkylations with hard carbon nucleophiles such as PhZnCl or

Grignard reagents follow mechanisms different from the palladium-catalyzed substitution of allylic acetates by stabilized enolates. It is similar to the mechanism of the Grignard cross-coupling, discussed before, and requires the formation of a bond between the transition metal atom of the catalyst and the nucleophile. The product is formed from this intermediate by a reductive elimination involving the approach of the nucleophile to the allylic moiety from the side of the π-coordinated metal (237, 262). The reaction was recently used to prepare olefins from allylic alcohol derivatives and Grignard reagents or organozinc reagents, with optical yields exceeding 97% e.e. (263–265).

H. Isomerization of Functionalized Olefins

The first transition-metal-catalyzed enantioselective olefin isomerization was reported in 1976 (262). Using a Rh/Diop catalyst, prochiral allylic alcohols were converted to optically active aldehydes with low e.e. More successful was the isomerization of allylamines for which the rearrangement of diethylgeranylamine to the corresponding enamine is an example (reaction[12]) (16, 266, 267, 334).



$$\mathrm{Me_2C{=}CH(CH_2)_2{-}\underset{\displaystyle Me}{\underset{|}{C}}{=}CHCH_2NEt_2 \rightarrow Me_2C{=}CH(CH_2)_2{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}CH{=}CHNEt_2} \qquad [12]$$

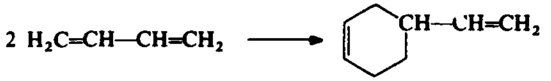
Such reactions can be catalyzed by Co and Rh catalysts of optically active phosphines (268, 269). However, the Rh/Binap system proved to be unrivaled in showing high catalytic activity and selectivity (270–272). With this catalyst, the optical induction in reaction [12] is virtually perfect (greater than 99% e.e.), provided that the starting material is stereoisomerically pure (with respect to the allylamine double bond). Hydrolysis of the enamine gives a "supernatural" citronellal with a much higher optical purity than natural citronellal, which has only 75–80% e.e. (150, 271). The enantioselective catalytic isomerization of diethylgeranylamine became the key step in the commercial synthesis of 1000 tons per year of the menthol (Takasago process), which represents approximately one-third of the present world production (150). The reaction proceeds via a nitrogen triggered 1,3 hydrogen shift in the allylamine part of diethylgeranylamine, without affecting the other double bond. The isomerization reaction can be extended to secondary allylamines, giving imines with high e.e. (266).

Recently, the enantioselective isomerization has also been applied to prochiral 4,7-dihydro-1,3-dioxepines. They rearrange to 4,5-dihydro-1,3-dioxepines with up to 25% e.e. on treatment with Ru/Diop and Rh/Diop complexes (273). In the isomerization of 3-methyl-5-phenyl-pent-2-ene with Ru/Diop catalysts only very low enantioselectivities were observed (274).

I. Olefin Dimerization

Depending on the type of olefin (monoolefin or diene) and on the type of reaction (involvement of one or different kinds of olefins) there are a number of variants of the olefin dimerization reaction (4, 7). In the early 1970s, Wilke, Bogdanovic, and co-workers used $[(\eta^3\text{-}C_3H_5)NiCl]_2/AlEtCl_2$/menthylphosphine catalysts for the reaction of 1,3-cyclooctadiene, norbornene, or norbornadiene with ethylene (hydrovinylation). They obtained optical inductions of up to 70–80% e.e. and they established the reaction mechanism (4, 7, 275, 276). It was recently shown that cyclohexadiene could be hydrovinylated with ethylene using Ni/Al/aminophosphine catalysts with 93% e.e. (277). The $[(\eta^3\text{-}C_3H_5)PdCl]_2$/phosphine systems have been shown to be active catalysts for isoprene dimerization leading to terpene derivatives (4, 7).

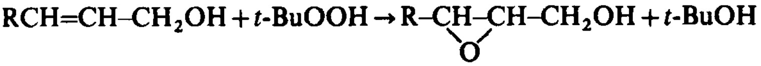
Olefin dimerization reactions frequently have low selectivity, giving rise to a range of products. This is evident in the dimerization of butadiene, which in addition to the chiral product 4-vinyl-1-cyclohexene, shown in eq. [13], invariably leads to 1,5-cyclooctadiene (103, 277, (278).



[13]

J. Oxidation

Carbon-to-carbon double bonds can be catalytically oxidized to epoxides with a variety of oxidants, for example, *tert*-butyl-hydroperoxide. If the C=C bond is part of an allylic alcohol system and titanium alkoxides/tartaric acid esters are used as enantioselective catalysts, the reaction is known as Sharpless epoxidation (eq. [14]).



$$RCH{=}CH{-}CH_2OH + t\text{-}BuOOH \rightarrow R{-}\underbrace{CH{-}CH}_{O}{-}CH_2OH + t\text{-}BuOH$$

[14]

Although the possibility of conducting the reaction with substoichiometric quantities of catalyst was mentioned in the first publications (280, 281), the standard procedures require stoichiometric quantities or even more of titanium alkoxide and tartaric acid ester. The many applications of the stoichiometric variant, including the industrial production of the pheromone disparlure (150), are not collected in this review.

Configurationally "inverse" epoxides or their ring-opened products can be obtained with $Ti(O\text{-}i\text{-}Pr)_4$/tartramide and $TiCl_2(O\text{-}i\text{-}Pr)_2$/diethyl tartrate epoxidation catalysts (282). The enantioselective oxidation with t-BuOOH and $Ti(O\text{-}i\text{-}Pr)_4$–tartaric acid esters can also be extended to the sulfide → sulfoxide reaction (57, 58, 283–287) and to the kinetic resolution of β-hydroxy amines via *N*-oxides (288). As extensive new reviews for these stoichiometric reactions are available (4, 17, 22, 49–56), they are not included inTables 2 and 3.

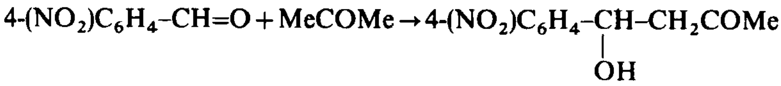
Recently, catalytic variants of the Sharpless epoxidation with substoichiometric quantities of catalyst and inductor have been described (53, 54, 289–291). Sharpless' catalytic procedure is based on the use of molecular sieves; this procedure facilitates the workup, and still gives optical inductions close to those of the stoichiometric systems (290). Similarly, the oxidation of sulfides can be carried out with substoichiometric amounts of catalysts (292).

Molybdenum complexes modified with optically active ligands have served as catalysts for the enantioselective epoxidation of olefins and the enantioselective oxidation of sulfides to sulfoxides both in stoichiometric (287, 293, 294) and catalytic reactions (287). Interestingly, the expoxidation of *p*-chlorostyrene with iodosylbenzene gave 50% e.e. using a basket-handle iron porphyrin catalyst (295, 296). The same optical induction was reported for the epoxidation with iron prophyrins chirally modified at the meso positions (297).

K. New Reaction Types

The extension of enantioselective transition metal catalysis to new reaction types is a challenging problem. In the following paragraphs reaction types are presented for which enantioselective catalysis has been demonstrated in the past few years.

1. Aldol Reaction. Enantioselective catalysis of the aldol reaction of p-nitrobenzaldehyde and acetone (eq. [15]) with Zn, Co, Ni, Cu, and Ru catalysts, modified with amino acid esters or quinine, was reported recently (298–300, 317).

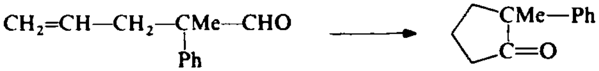


$$4\text{-}(NO_2)C_6H_4\text{-}CH{=}O + MeCOMe \rightarrow 4\text{-}(NO_2)C_6H_4\text{-}\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}CH_2COMe$$

[15]

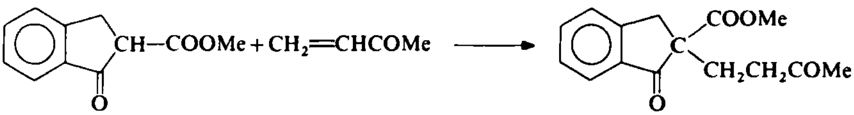
The best results were obtained with the Zn(II)/TyrOEt system, using 16 mol% of catalyst. Addition of β-cyclodextrin proved beneficial (299). The optical purity of the product is unknown. The relevance of the model reaction (eq. [15]) lies in the fact that aldol reactions in biological systems are catalyzed by aldolase enzymes containing Zn^{2+} at the active sites (301). Another enantioselective aldol reaction of nitrobenzaldehydes with cyanomethyltributyltin has been reported. Palladium–Diop catalysts gave the aldol product in up to 34% e.e. (302).

2. *Hydroacylation.* Recently, two examples of the hydroacylation of a C=C bond were described (303, 304). One of these, the intramolecular cyclization of an α,β-unsaturated aldehyde, is shown in eq. [16]. The cyclization product is formed in up to 69% e.e. when the catalyst is $[Rh(Chiraphos)_2]Cl$. Under conditions of kinetic resolution, the unreacted aldehyde is optically pure (304).



[16]

3. *Michael Addition.* The catalyst $Ni(acac)_2$ has been successfully utilized in Michael reactions with an increase in yield with respect to the usual base catalysis due to the mild reaction conditions. An example is the addition of the racemization-labile C–H bond of methyl 1-indanone-2-carboxylate to vinyl methyl ketone shown in eq. [17].



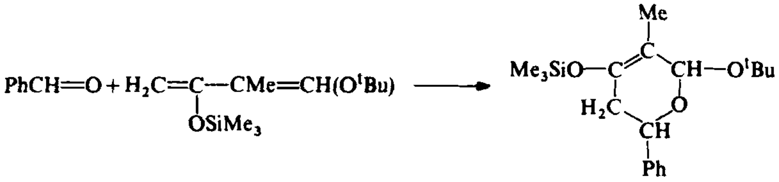
[17]

The addition product bearing a configurationally stable quarternary asymmetric center was formed in 66% e.e. when an *in situ* catalyst consisting of the components $Co(acac)_2$ and 1,2-diamino-1,2-diphenylethane was used at low temperatures (305). Similarly, aniline was added enantioselectively to chalcone with copper catalysts containing Schiff bases and enamino ketones (306).

4. *Amino Acid Syntheses.* New amino acid syntheses of different types were reported recently. The nitro group in racemic 3-nitrocaprolactame was reduced with hydrogen. The catalyst $PdCl_2$/1-phenylethylamine gave the corresponding amino derivative which was hydrolyzed to L-lysine in 11% optical yield (307). Work on amino acid synthesis by the reductive aminolysis of azlactones with the same catalyst continued (308, 309, 326). The new

enantioselective allylation of the Schiff base of methyl glycinate and benzophenone is described in Section III-G (261).

5. Cyclocondensation. Traces of lanthanide complexes catalyze the cyclocondensation of activated dienes with aldehydes. In the reaction of siloxy-substituted dienes with benzaldehyde (eq. [18]) Eu(hfc)$_3$ induces inductions of up to 58% e.e. in the addition product, which can be degraded to substituted β-hydroxy esters (310).



[18]

6. Oxidative Cyclization. 2-Allyl substituted phenols are cyclized on catalytic oxidation with *t*-BuOOH or Cu(OAc)$_2$/O$_2$ (7, 311, 312), (η^3-pinenyl)Pd catalysts giving dihydrobenzofurans in up to 26% e.e. α,ω-Diols were dehydrogenated to lactones by Rh/Diop catalysts with up to 29% e.e. (313, 318).

7. Other Reaction Types. OsO$_4$/Bovine serum albumin catalyzes the *cis*-dihydroxylation of olefins, such as styrene or α-methylstyrene, by *t*-BuOOH in up to 68% e.e. (314). The isomerization of allylamines (266–272), the reduction of cyclic anhydrides to lactones (106, 171, 172), the hydrogenation of olefins catalyzed by Pd/methyl viologen and enzymes (157), the hydrosilylation of oximes (211, 212), and the opening of epoxide rings by thiols with the heterogeneous catalyst zinc tartrate (72) have been mentioned earlier. Since the last summaries (4, 7, 315), no further enantioselective hydrocyanations have been reported.

IV. TABLE 2: THE OPTICALLY ACTIVE LIGANDS 1–329

Table 2 is a parade of all the optically active compounds **1–329** used as ligands in enantioselective transition metal catalysts in 1984–1986 starting with the rather trivial cases of amino acid derivatives. Knowledge of the structures and configurations of the optically active ligands given in Table 2 is a prerequisite for the correlation of the configuration of the products (Table 3) and the ligands used in the catalysts. The ligands **1–311** are arranged according to their molecular formula, $C_xH_yA_z \cdots$ each page. Each ligand is characterized by a boldface number, except for the "name" ligands in Table 1, which are specified additionally by the accepted acronyms used throughout the review. Following the boldface number, the configurational symbol, the optical rotation (D-line), and the particular designation of each ligand are given, provided this information is available in the references under review. For each ligand, all the references which describe its application in the report period are enumerated in parentheses. The references are italicized if details of the synthesis and characterization of the ligand are given.

The ligands are depicted in Table 2 as their parent compounds. This means that the tartrate anion designated (TA-2H$^+$) is to be found in Table 2 under the tartaric acid TA entry and the anion of a salicylaldimine, for example, (**44**-H$^+$), in the entry for the corresponding protonated compound **44**.

At the end of Table 2, the polymer ligands **312**–**329**, described in the period covered in this report, are given. Because there is only a limited number of such systems, their arrangement is arbitrary.

V. TABLE 3: THE ENANTIOSELECTIVE CATALYSTS AND THE OPTICALLY ACTIVE PRODUCTS

All the optically active compounds (about 350), prepared in 1984–1986 by enantioselective catalysis with transition metal complexes, are collected in Table 3. They are classified in column 1 according to their molecular formulas. Their structural formulas are given in column 2 in a two-line presentation in which the newly formed asymmetric center is set off by a boldface letter.

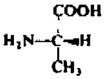
In column 3 (enantioselective catalyst) the first entry is reserved for the catalyst that gives the highest optical induction for the specific product reported in the reference under discussion. All the other less efficient ligands and metals tested in the same reference follow in an arbitrary order. Thus column 3 provides a survey of the catalyst types. For products such as *N*-acetylphenylalanine, methyl *N*-acetylphenylalaninate, *N*-acetylalanine, or ethyl 3-hydroxybutanoate, column 3 is a parade of the catalysts. The boldface numbers of the ligands refer to Table 2. If the enantiomer of a ligand depicted in Table 2 is used, this is indicated by a primed boldface number or ligand abbreviation. A diastereomer of a ligand from Table 2 is designated by a doubly primed ligand number. For *in situ* catalysts, the procatalyst and the cocatalyst are separated by a slash.

In column 4 the maximum optical induction obtained in a specific paper is reported together with the configuration of the newly formed asymmetric center of the product shown in column 2. The predominant configuration of the product and the configuration of the optically active ligand used in the catalyst can be correlated with the help of Table 2. The optical induction is given as enantiomeric excess e.e. (or diastereomeric excess d.e., when optically

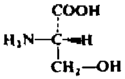
(*text continued on page* 236)

Table 2

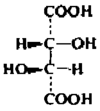
The Optically Active Ligands 1–329 Used to Prepare Enantioselective Transition Metal Catalysts, Recorded in *CA Selects* "Catalysis (Organic Reactions)," Jan. 1, 1984 Through Oct. 20, 1986.



1: L-(+)-Alanine (178)

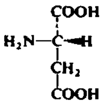


2: L-(−)-Serine (178)

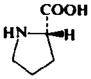


3: (*R*, *R*)-(+)-Tartaric acid, *TA* (69, 71, 173–177, 181–186)

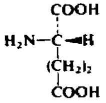
$C_4H_7 \cdots$



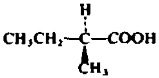
4: L-(+)-Aspartic acid (178)



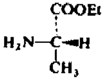
5: L-(−)-Proline (178)



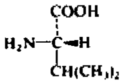
6: L-Glutamic acid (178)



7: (*R*)-(−) (156)

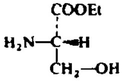


8: L-AlaOEt (298)

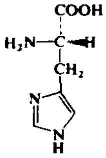


9: L-(+)-Valine (178)

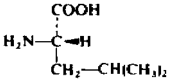
C_5H_{11}



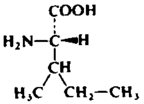
10: L-SerOEt (*300*)



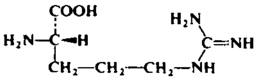
11: L-Histidine (178)



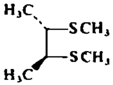
12: L-(−)-Leucine (178)



13: L-Isoleucine (137)

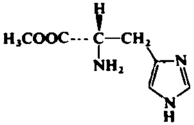


14: L-Arginine (178)

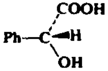


15: (*S*, *S*) (*238*)

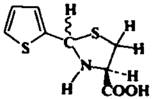
$C_7H_{11}\cdots$



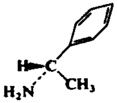
16: L-HisOMe (*298*)



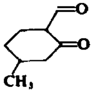
17: (*R*)-(−)-Mandelic acid (167)



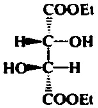
18: (4*R*)-(−) (*60*)



19: (*S*)-(−) (307–309)

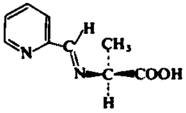


20: (306)

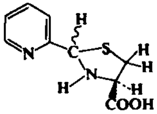


21: (*R*, *R*)-(+)-Diethyl tartrate, DET (287, 290)

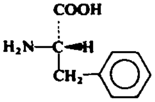
$C_9H_{10}\cdots$



22: (*S*)-(+) (*210*)

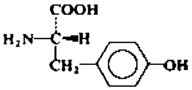


23: (4*R*)-(−) (*60*)

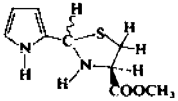


24: (*S*)-Phenylalanine (178, 182)

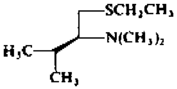
Table 2 (Contd)



25: L-Tyrosine (*178*)

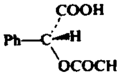


26: (4*R*)-(−) (*60*)

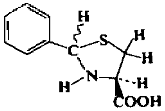


27: (*S*) (*238*)

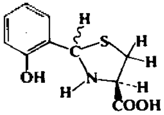
$C_{10}H_{10}$ · · ·



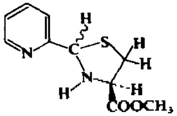
28: (*R*)-(−) (*167*)



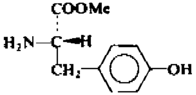
29: (4*R*)-(−) (*60*)



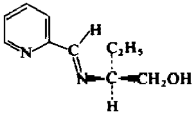
30: (4*R*)-(−) (*60*)



31: (4*R*)-(−) (*59*, *60*)

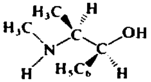


32: (*S*)-(+)-TyrOMe (298, 300)

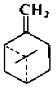


33: (*S*)-(+) (*210*)

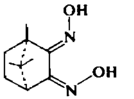
$C_{10}H_{15}$ · · ·



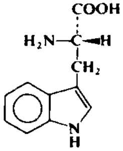
34: (2*S*, 3*S*)-(−) (229)



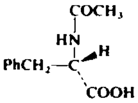
35: β-Pinene (312)



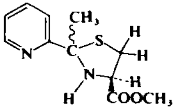
36: (−)-α-CqdH (71)



37: L-Tryptophan (178)

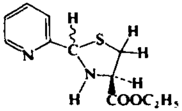


38: L-(+) (*120*)

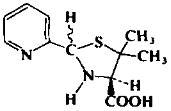


39: (4*R*)-(+)-Pythia (*60*, 212)

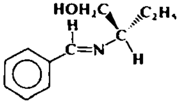
$C_{11}H_{14}$ · · ·



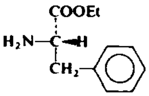
40: (4*R*)-(−) (*60*)



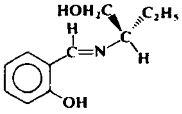
41: (4*R*)-(−) (*60*)



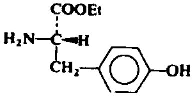
42: (*S*)-(+) (*229*)



43: L-PheOEt (300)

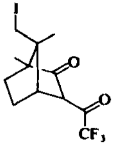


44: (*S*)-(+) (*229*)

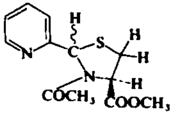


45: (*S*)-(+)-TyrOEt (300)

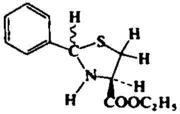
$C_{12}H_{14}$ · · ·



46: IodofacamH (*78*)

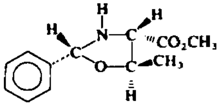


47: (4*R*)-(+) (*60*)

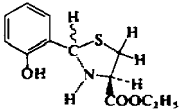


48: (4*R*) (*60*)

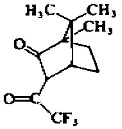
Table 2 (Contd)



49: (2*R*, 4*S*, 5*R*) (*229*)

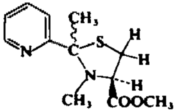


50: (4*R*)-(−) (*60*)

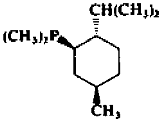


51: TfcH (78, 195)

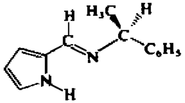
$C_{12}H_{16}\cdots$



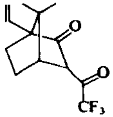
52: (4*R*)-(+) (*60*)



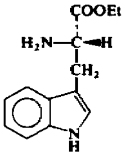
53: (−)-MDMP (161, 168)



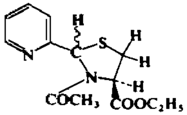
54: (*S*)-(+) (*210*, 229)



55: 10-MethylenefacamH (*78*)

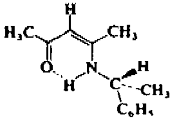


56: L-TrpOEt (300)

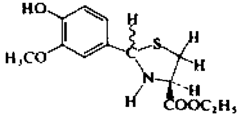


57: (4*R*)-(+) (*60*)

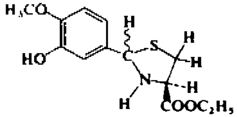
$C_{13}H_{17}\cdots$



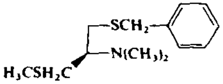
58: (*R*)-(−) (*123, 229*)



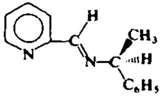
59: (4*R*) (*60*)



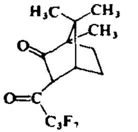
60: (4*R*) (*60*)



61: (*S*) (*238*)

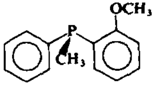


62: (*S*)-(+) (*210*, *212*, *229*)

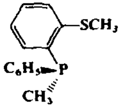


63: HfcH (195, 310)

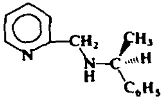
$C_{14}H_{15}$ · · ·



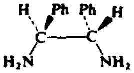
64: PAMP (261)



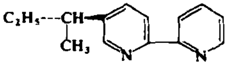
65: (*R*)-(+) (104)



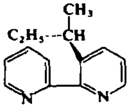
66: (*S*)-(−) (*210*)



67: (*R*, *R*)-(+) (305)

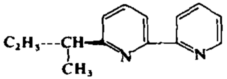


68: (*S*)-(+) (192)

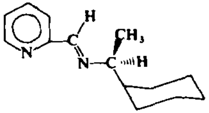


69: (*S*)-(−) (192)

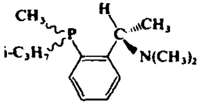
$C_{14}H_{16}$ · · ·



70: (*S*)-(+) (192)

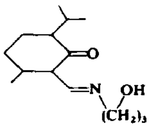


71: (*S*)-(+) (*210*)

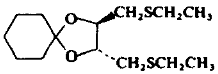


72: (S_C)-(−) (104)

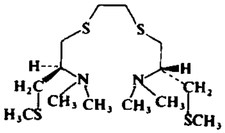
Table 2 (Contd)



73: (*306*)

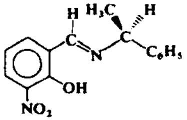


74: (*R*, *R*) (*238*)

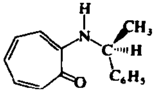


75: (*S*, *S*) (*238*)

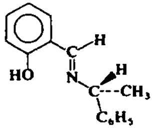
$C_{15}H_{14}\cdots$



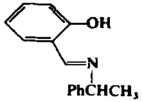
76: (*S*)-(+) (*229*)



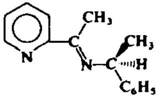
77: (*S*)-(−) (*208*, *229*)



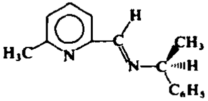
78: (*R*)-(−) (*123*, *229*)



79: (306)

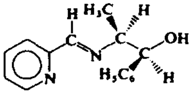


80: (*S*)-(+) (*210*)

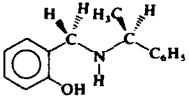


81: (*S*)-(+) (*210*)

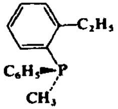
$C_{15}H_{16}\cdots$



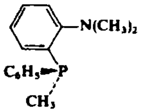
82: (*S*, *S*) (*229*)



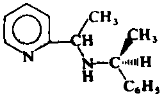
83: (*S*)-(+) (*229*)



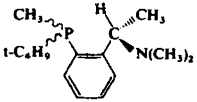
84: (*R*)-(−) (104)



85: (*R*)-(+) (104)

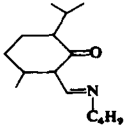


86: (*S*)-(+) (*210*)

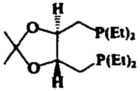


87: (S_C)-(−) (104)

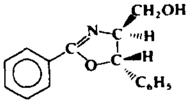
$C_{15}H_{27}\ldots$



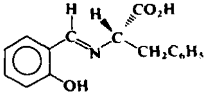
88: (306)



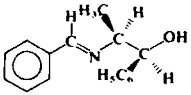
89: (−)-Et-Diop (271)



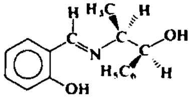
90: (*S*, *S*) (*229*)



91: (*S*) (*229*)

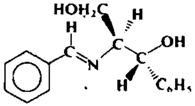


92: (*S*, *S*) (*229*)

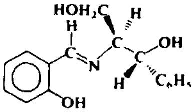


93: (*S*, *S*)-(−) (*229*)

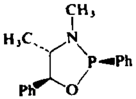
$C_{16}H_{17}\ldots$



94: (*R*, *S*)-(+) (*229*)

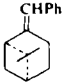


95: (*R*, *S*)-(+) (*229*)

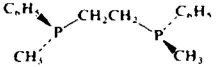


96: (2*R*, 4*S*, 5*R*)-(+)-Oxazaphos (261)

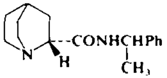
Table 2 (Contd)



97: Ph-β-Pinene (312)

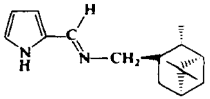


98: (*S*)-(−) (104)

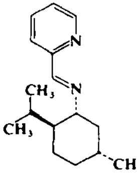


99: (*R*, *R*)-QC (*138*)

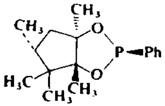
$C_{16}H_{24}$ · · ·



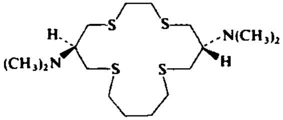
100: (1*R*, 2*R*, 3*R*)-(−) (*210*)



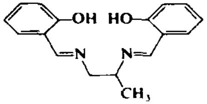
101: (1*R*, 3*R*, 4*S*) (279)



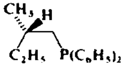
102: (2*S*, 4*S*, 5*R*)-(+)-Dioxaphos (261)



103: (*R*, *R*)-(−) (*239*)

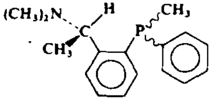


104: (306)

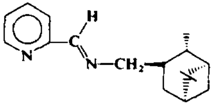


105: (*S*)-(+) (170)

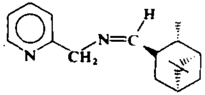
$C_{17}H_{22}$ · · ·



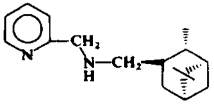
106: (S_C)-(−) (104)



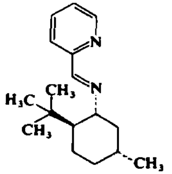
107: (1*R*, 2*R*, 3*R*)-(−) (*59*, *210*)



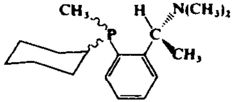
108: (1*R*, 2*R*, 3*R*)-(−) (*210*)



109: (1*R*, 2*R*, 3*R*)-(−) (*210*)

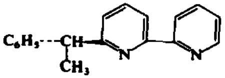


110: (1*R*, 3*R*, 4*S*) (279)

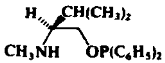


111: (R_C)-(+) (104)

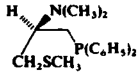
$C_{18}H_{16}\cdots$



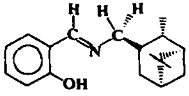
112: (*S*)-(+) (*192*)



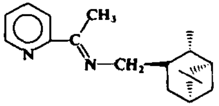
113: (*S*)-ValNHOP (*205*)



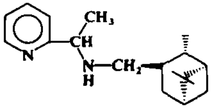
114: (*S*)-(+)-Methylcysphos (*240*)



115: (1*R*, 2*R*, 3*R*)-(−) (*229*)

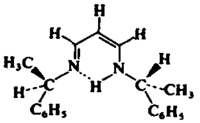


116: (1*R*, 2*R*, 3*R*)-(−) (*210*)

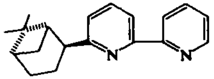


117: (1*R*, 2*R*, 3*R*)-(−) (*210*)

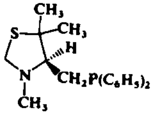
$C_{19}H_{22}\cdots$



118: (*R*, *R*) (*123*)

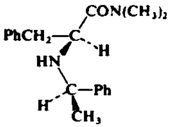


119: (1*S*, 2*S*)-(+) (*192*)

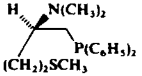


120: (*R*)-Cyclopenphos (*240*)

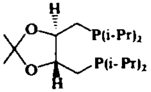
Table 2 (Contd)



121: (*S*, *R*)-Pha (138)

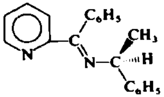


122: (*S*)-(−)-Methphos (*240*)

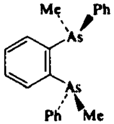


123: (−)-*i*-Pr-Diop (271)

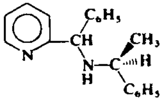
$C_{20}H_{18}\cdots$



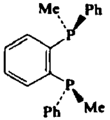
124: (*S*)-(−) (*210*)



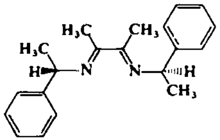
125: (*S*, *S*)-Dias (118)



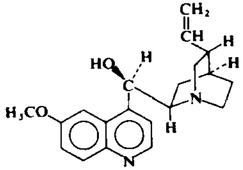
126: (*S*)-(−) (*210*)



127: (*S*, *S*)-Diph (118)

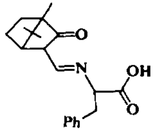


128: (*R*, *R*) (*210*, *278*)

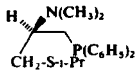


129: (−)-Quinine (138, 298)

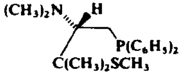
$C_{20}H_{25}$ · · ·



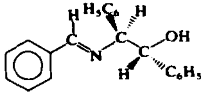
130: (306)



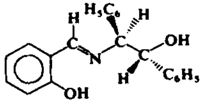
131: (*S*)-(−)-*i*-Propylcysphos (*240*)



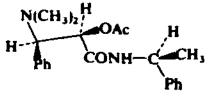
132: (*R*)-(−)-*S*-Methylpenphos (*240*)



133: (*S*, *S*) (*229*)

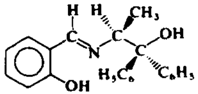


134: (*S*, *S*)-(+) (*229*)

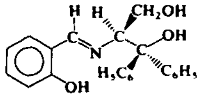


135: (2*R*, 3*R*)-*S*-DHP-OAc (138)

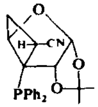
$C_{22}H_{21}$ · · ·



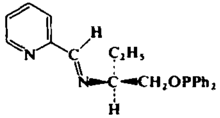
136: (*S*) (*229*)



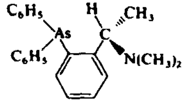
137: (*S*)-(−) (*229*)



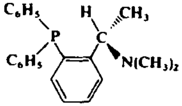
138: (1*R*, 3*R*, 4*S*, 5*R*, 6*R*)-(+) (*128*)



139: (*S*)-(−) (*210*)



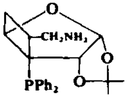
140: (*S*)-(−) (104)



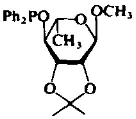
141: (*S*)-(−) (104)

Table 2 (Contd)

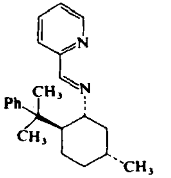
$C_{22}H_{26}\cdots$


O
CH₂NH₂
O
PPh₂
O

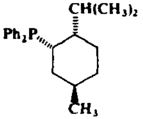
142: (1*R*, 3*R*, 4*S*, 5*R*, 6*R*)-(+) (*128*)


Ph₂PO
O
OCH₃
CH₃
O
O

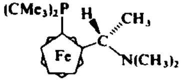
143: L-(−) (*107*)


N
N
Ph
CH₃
CH₃
CH₃

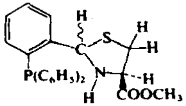
144: (1*R*, 3*R*, 4*S*) (279)


CH(CH₃)₂
Ph₂P
CH₃

145: (+)-NMDPP (137, 147, *151*, *161*, *168*, 191, *265*)

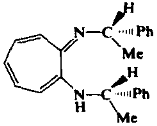

(CMe₃)₂P
H
CH₃
C
Fe
N(CH₃)₂

146: (S_C, R_{Fc})-(+) (112)

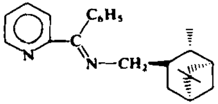

H
C
S
H
H
P(C₆H₅)₂
N
H
H
COOCH₃

147: (4*R*)-(−) (*60*)

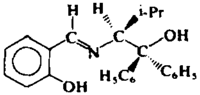
$C_{23}H_{24}\ldots$


H
N
C
Ph
Me
H
N
C
Ph
H
Me

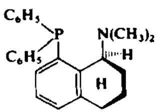
148: (*S*, *S*)-(−) (*208*)

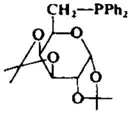

N
C₆H₅
C
N
CH₂

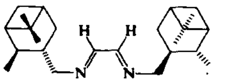
149: (1*R*, 2*R*, 3*R*)-(−) (*210*)

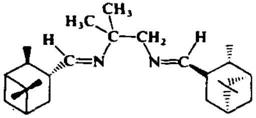

H
H
i-Pr
C
N
C
OH
C
OH
H₅C₆
C₆H₅

150: (*S*) (*229*)

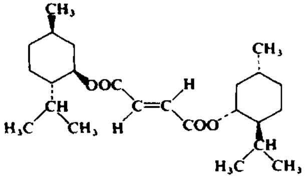

151: (*S*)-(+) (104)

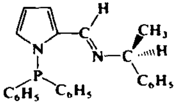

152: (−)-GDPP (161, 168)

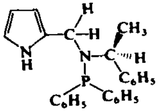

153: (1*S*, 2*S*, 3*S*, 5*R*)-(+) (*278*)

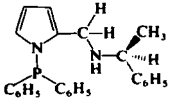

154: (1*R*, 2*R*, 3*R*)-(−) (*210*)

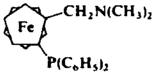
$C_{24}H_{29}$ · · ·

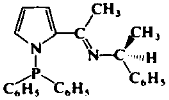

155: (1*R*, 3*R*, 4*S*)-(−)
Dimenthyl fumarate (233)


156: (*S*)-(−) (*207*, 241)

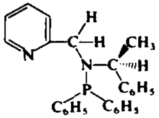

157: (*S*)-(−) (*207*, 241)


158: (*S*)-(−) (*207*)


159: (+)-FeNP (206)


160: (*S*)-(+) (*207*, 241)

$C_{26}H_{25}$ · · ·


161: (*S*)-(−) (*207*, 241)

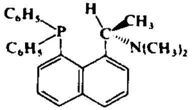
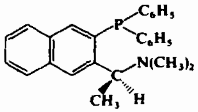
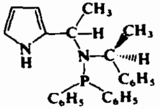

162: (*R*)-(+) (104)

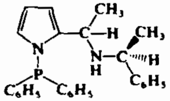
Table 2 (Contd)



163: (*S*)-(−) (104)

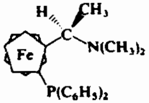


164: (*S*)-(−) (*207*, 241)

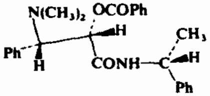


165: (*S*)-(−) (*207*)

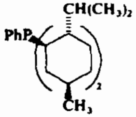
$C_{26}H_{28}$ · · ·



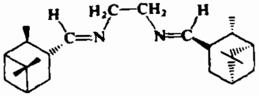
166: (R_C, S_{Fc})-(−)-PPFA (215, 216)



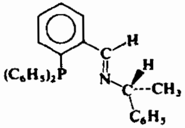
167: (2*S*, 3*S*)-*R*-DHP-OBz (138)



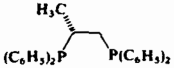
168: DMPP (191, 265)



169: (1*R*, 2*R*, 3*R*)-(−) (*210*)

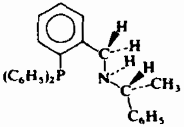


170: (*R*)-(+)-Iminphos (*122*, 229)

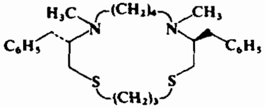


171: (*R*)-(+)-Prophos (108, 121, 125, 193, 194, 197, 212, 244, 250, 261)

$C_{27}H_{26}$ · · ·



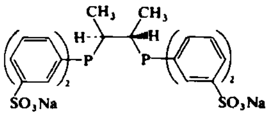
172: (*R*)-(+)-Aminphos (*122*)



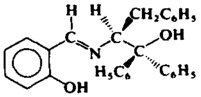
173: (*S*, *S*) (*239*)

$(EtO)_3Si{-}CH_2{-}PMen_2$

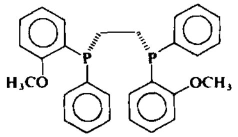
174: (1*R*, 3*R*, 4*S*)-(−) (*74*)



175: (*S*, *S*)-(−) (*132*)

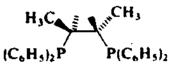


176: (*S*) (*229*)

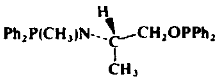


177: (*R*, *R*)-(−)-Dipamp (100, 135, 148, 149, 151, 154, 160, 244, 250, 256, 261)

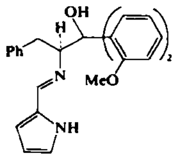
$C_{28}H_{28}$ · · ·



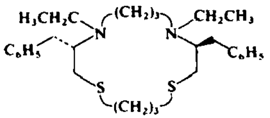
178: (*S*, *S*)-(−)-Chiraphos (125, 131, 160, 171, 193, 194, 224, 244, 250, 251, 258, 261, 264, 265, 303)



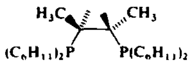
179: (*S*)-AlaNOP (130, *205*, 277)



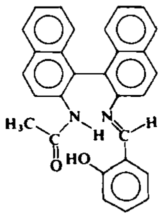
180: (*S*) (232)



181: (*S*, *S*) (*239*)



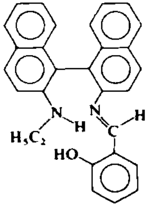
182: (*S*, *S*)-(+)-Cy-Chiraphos (*165*)



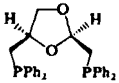
183: (*S*)-(−) (*229*)

Table 2 (Contd)

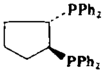
$C_{29}H_{24}\cdots$



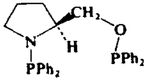
184: (*S*)-(−) (*229*)



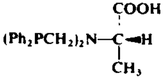
185: (*R*, *S*)-Dioxop (116)



186: (*S*, *S*)-(−)-Dpcp (*64*)

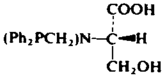


187: (*S*)-(+)-ProNOP (103, 130, *205*)



$(Ph_2PCH_2)_2N-\overset{\displaystyle COOH}{\underset{\displaystyle CH_3}{C}}-H$

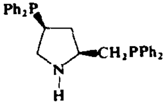
188: (*S*) (105)



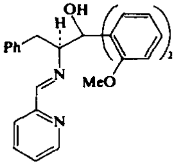
$(Ph_2PCH_2)N-\overset{\displaystyle COOH}{\underset{\displaystyle CH_2OH}{C}}-H$

189: (*S*) (105)

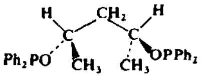
$C_{29}H_{29}\cdots$



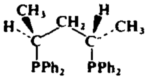
190: (−)-PPM (212)



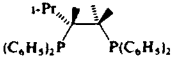
191: (*S*) (232)



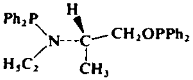
192: (*R*, *R*)-BDPOP (65, 66, 110, 187)



193: (*S*, *S*)-(−)-BDPP (*65*, 66)

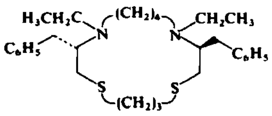


194: (*R*)-(+)-Valphos (187, 240)

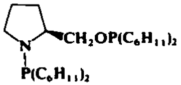


195: (*S*) (130)

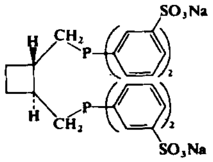
$C_{29}H_{44}$ · · ·



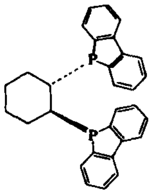
196: (*S*, *S*) (*239*)



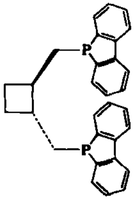
197: (*S*)-Cy-ProNOP (130)



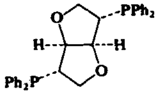
198: (*S*, *S*)-(+) (*132*)



199: (*S*, *S*) (227)

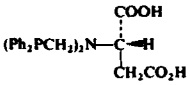


200: (*R*, *R*) (227)

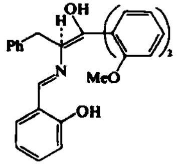


201: (*S*, *S*)-(+) (*115*)

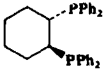
$C_{30}H_{29}$ · · ·



202: (*S*) (105)

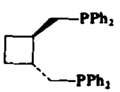


203: (*S*) (232)

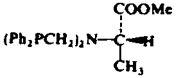


204: (*S*, *S*) (227)

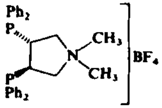
Table 2 (Contd)



205: (*R*, *R*)-Cyclobutane-Diop (227, 135)

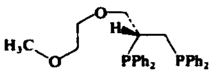


206: (*S*) (105)

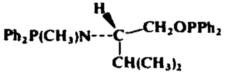


207: (*R*, *R*) (*63*)

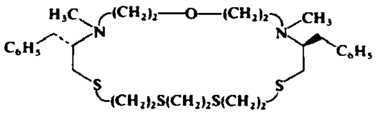
$C_{30}H_{32}$ · · ·



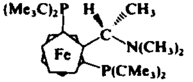
208: D-(+) (*127*)



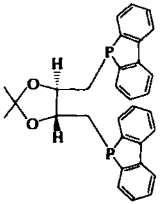
209: (*S*)-ValNOP (130, *205*, 277)



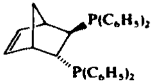
210: (*S*, *S*) (*239*)



211: (S_C, R_{Fe})-(−) (*112*)

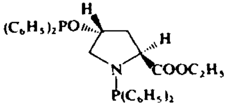


212: (*R*, *R*) (227)

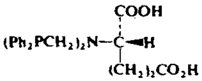


213: (*R*, *R*)-(−)-Norphos (121, 123, 125, 135, 197, 208, 209, 210, 212, 244, 250, 261)

$C_{31}H_{31}$ · · ·

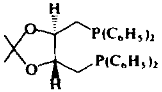


214: (2*S*, 4*R*)-*E*-ProNOP (130, *205*)

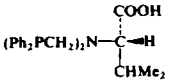


$(Ph_2PCH_2)_2N\text{—}\overset{COOH}{\underset{(CH_2)_2CO_2H}{C}}\text{—}H$

215: (*S*) (105)

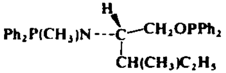


216: (*R*, *R*)-(−)-Diop (70, 100, 103, 108, 111, 114, 120, 121, 125, 128, 129, 131, 135, 136, 145, 149, 151, 154, 155, 156, 158, 160, 163, 172, 187, 194, 196, 197, 208–213, 222, 224, 227, 228, 256, 258, 259, 261, 265, 271, 273, 274, 302, 313)



$(Ph_2PCH_2)_2N\text{—}\overset{COOH}{\underset{CHMe_2}{C}}\text{—}H$

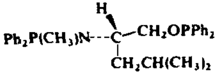
217: (*S*) (105)



$Ph_2P(CH_3)N\text{---}\overset{H}{\underset{CH(CH_3)C_2H_5}{C}}\text{—}CH_2OPPh_2$

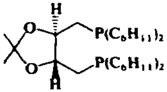
218: (*S*, *S*)-IleuNOP (130)

$C_{31}H_{35}$ · · ·



$Ph_2P(CH_3)N\text{---}\overset{H}{\underset{CH_2CH(CH_3)_2}{C}}\text{—}CH_2OPPh_2$

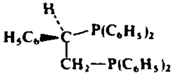
219: (*S*)-LeuNOP (130)



220: (*R*, *R*)-(−)-Cy-Diop (*165*, 271)

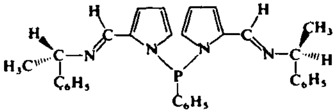
$(EtO)_3Si\text{—}(CH_2)_5\text{—}PMen_2$

221: (1*R*, 3*R*, 4*S*)-(−) (*74*)

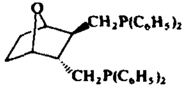


$H_5C_6\text{—}\overset{H}{\underset{CH_2\text{—}P(C_6H_5)_2}{C}}\text{—}P(C_6H_5)_2$

222: (*R*)-Phenphos (187, 244)



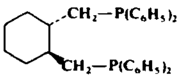
223: (*S*, *S*) (*207*)



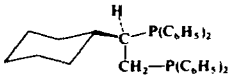
224: (−) (113)

Table 2 (Contd)

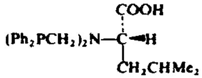
$C_{32}H_{34}$ · · ·



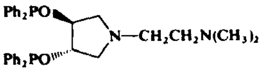
225: (1*S*, 2*S*)-(+)-DIPMC (261)



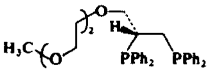
226: (*R*)-Cycphos (244)



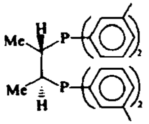
227: (*S*) (105)



228: (3*S*, 4*S*)-(+)-POP-AE (*119*, 152, 153)

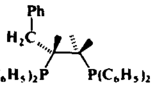


229: D-(+) (*127*)

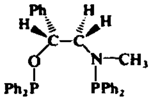


230: (*S*, *S*)-Metachiraphos (*250*)

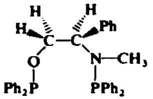
$C_{33}H_{30}$ · · ·



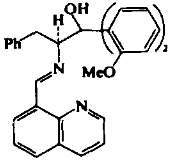
231: (*R*)-(+)-Benzphos (187)



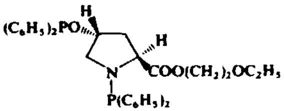
232: (*R*)-(+) (*98*)



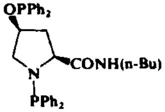
233: (*R*) (*98*, *103*, 130, 277)



234: (*S*) (232)

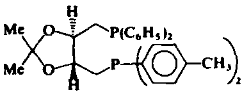


235: (2*S*, 4*R*)-*EE*-ProNOP (130, *205*)



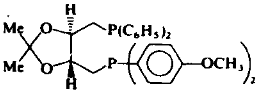
236: Bu-ProNOP (130)

$C_{33}H_{36}$ · · ·



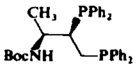
Me
Me
H
H
P(C6H5)2
P
CH3
2

237: (*R*, *R*)-(−) (*114*)



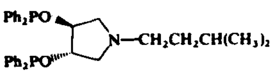
Me
Me
H
H
P(C6H5)2
P
OCH3
2

238: (*R*, *R*)-(−) (*114*)



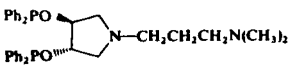
CH3
PPh2
BocNH
PPh2

239: (2*R*, 3*S*) (*109*)



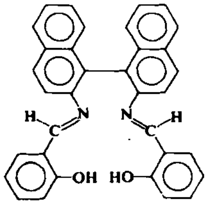
Ph2PO
Ph2PO
N—CH2CH2CH(CH3)2

240: (3*S*, 4*S*)-(+)-POP-IP (*119*, 152, 153)



Ph2PO
Ph2PO
N—CH2CH2CH2N(CH3)2

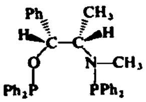
241: (3*S*, 4*S*)-(+)-POP-AP (*119*, 152, 153)



H
N
N
H
C
C
OH
HO

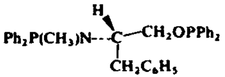
242: (*S*) (*229*)

$C_{34}H_{33}$ · · ·



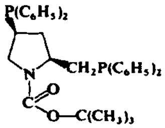
Ph
CH3
H
H
C
C
O
N—CH3
Ph2P
PPh2

243: (1*R*, 2*S*)-(+) (*98*, *102*, *103*, 130, *205*)



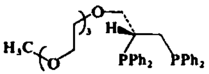
H
Ph2P(CH3)N
C
CH2OPPh2
CH2C6H5

244: (*S*)-PheNOP (*102*, *126*, 130, 277)



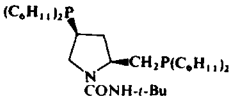
P(C6H5)2
CH2P(C6H5)2
N
C
O
O—C(CH3)3

245: (2*S*, 4*S*)-(−)-BPPM (70, 76, 154, 167, 259, 261, 271, 302)



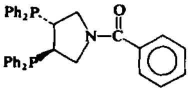
H3C
O
O
3
H
PPh2
PPh2

246: D-(+) (*127*)



(C6H11)2P
CH2P(C6H11)2
N
CONH-t-Bu

247: (*S*, *S*)-(−) (*166*)

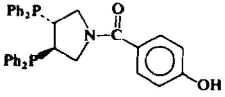


Ph2P
Ph2P
N
C
O

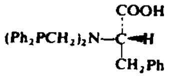
248: (*R*, *R*)-(+)-Benzoylpyrphos (*61*)

Table 2 (Contd)

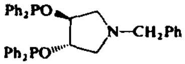
$C_{35}H_{31}\cdots$


Ph₂P
Ph₂P
N
C
O
OH

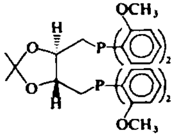
249: (*R*, *R*) (*61*)


COOH
(Ph₂PCH₂)₂N—C—H
CH₂Ph

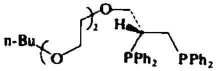
250: (*S*) (105)


Ph₂PO
Ph₂PO
N—CH₂Ph

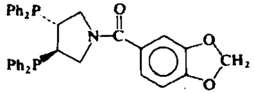
251: (*S*, *S*)-(+)-POP-BZ (*152*)


OCH₃
H
O
O
P
P
H
OCH₃
2
2

252: (*R*, *R*)-PAMPOP (256)

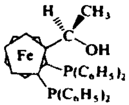

n-Bu
O
O
2
H
PPh₂
PPh₂

253: D-(+) (*127*)

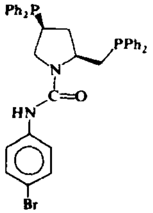

Ph₂P
Ph₂P
N
C
O
O
O
CH₂

254: (*R*, *R*) (61)

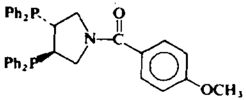
$C_{36}H_{32}\cdots$


H
CH₃
C
OH
Fe
P(C₆H₅)₂
P(C₆H₅)₂

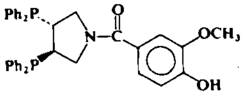
255: (R_C, S_{Fc})-BPPFOH (259)


Ph₂P
PPh₂
N
C=O
HN
Br

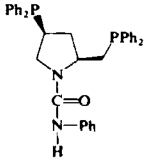
256: *p*-Br-C_6H_4CAPP (154)


Ph₂P
Ph₂P
N
C
O
OCH₃

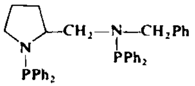
257: (*R*, *R*) (*61*)



258: (*R*, *R*) (61)

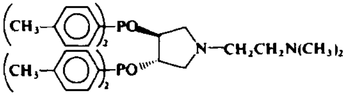


259: Ph-CAPP (154)

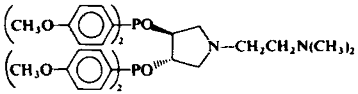


260: (*S*)-(−) (*99*)

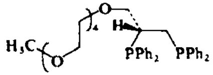
$C_{36}H_{44}$ · · ·



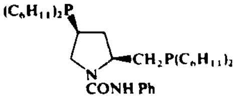
261: (3*S*, 4*S*)-(+)-*p*-Me-POP-AE (*119*, 152)



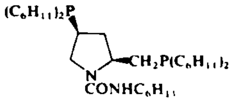
262: (3*S*, 4*S*)-(+)-*p*-MeO-POP-AE (*119*, 152, 153)



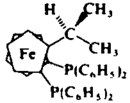
263: D-(+) (*127*)



264: (2*S*, 4*S*)-(−) (*166*)

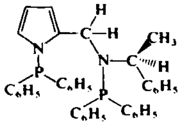


265: (2*S*, 4*S*)-(−) (*166*)

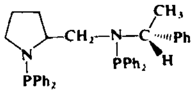


266: (*S*)-BPPF-Me (259)

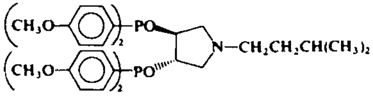
$C_{37}H_{38}$ · · ·



267: (*S*)-(−) (*207*, 241)

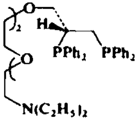


268: (*S*, *R*)-(+) (*99*)

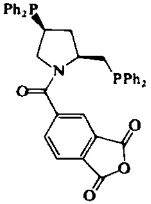


269: (3*S*, 4*S*)-(+)-*p*-MeO-POP-IP (152, 153)

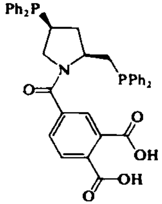
Table 2 (Contd)


H
PPh₂
PPh₂
N(C₂H₅)₂

270: D-(+) (*127*)

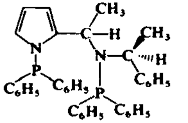


271: (2*S*, 4*S*)-(−) (*134*)

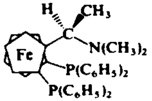

Ph₂P
N
PPh₂
OH
OH

272: (2*S*, 4*S*)-(−) (*134*)

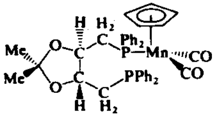
$C_{38}H_{36}$ · · ·


CH₃
CH₃
H
C₆H₅

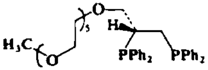
273: (*S*)-(−) (*207*, 241)


H
CH₃
Fe
N(CH₃)₂
P(C₆H₅)₂
P(C₆H₅)₂

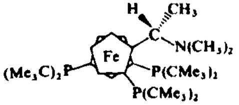
274: (R_C, S_{Fc})-(−)-BPPFA (121, 125, 197, 209, 212, 259)


Me
Me
Ph₂
Mn
CO
CO
PPh₂

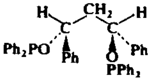
275: (*R*, *R*)-(−)-CpMn(CO)₂-Diop (*124*, 125)


H₃C
H
PPh₂
PPh₂

276: D-(+) (*127*)

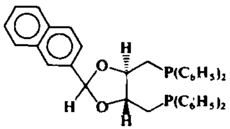

H
CH₃
(Me₃C)₂P
Fe
N(CH₃)₂
P(CMe₃)₂
P(CMe₃)₂

277: (S_C, S_{Fc})-(−) (*112*)

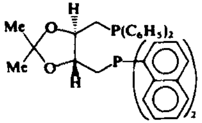

H
CH₂
H
Ph₂PO
Ph
Ph
PPh₂

278: (*R*, *R*)-(−)-BDPODP (66, *110*, 187)

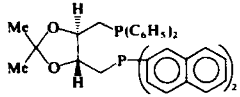
C$_{39}$H$_{39}$ · · ·



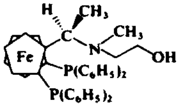
279: (*R*, *R*)-(−) (*114*)



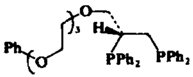
280: (*R*, *R*)-(−) (*114*)



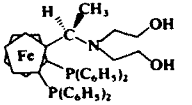
281: (*R*, *R*)-(−) (*114*)



282: (R_C, S_{Fc})-BPPF-NMeCH$_2$CH$_2$OH (259)

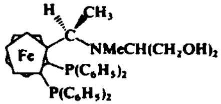


283: D-(+) (*127*)

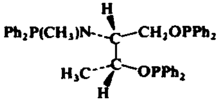


284: (R_C, S_{Fc})-BPPF-N(CH$_2$CH$_2$OH)$_2$ (259)

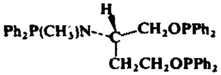
C$_{40}$H$_{41}$ · · ·



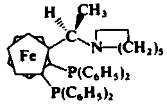
285: (R_C, S_{Fc})-BPPF-NMeCH(CH$_2$OH)$_2$ (259, 260)



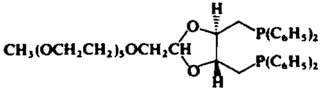
286: (2*R*, 3*R*)-(+)-Threophos (*277*)



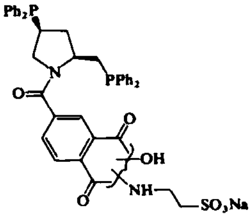
287: (*S*) (277)



288: (R_C, S_{Fc})-BPPF-N(CH$_2$)$_5$ (259)



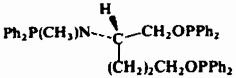
289: (*R*, *R*)-PGE-6-Diop (133)



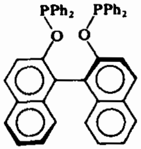
290: (2*S*, 4*S*)-(−) (134)

Table 2 (Contd)

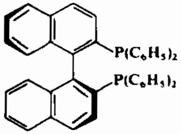
$C_{42}H_{42}$ · · ·


H
Ph₂P(CH₃)N
C
CH₂OPPh₂
(CH₂)₂CH₂OPPh₂

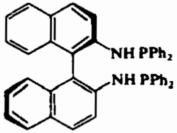
291: (*S*) (277)


PPh₂
PPh₂
O
O

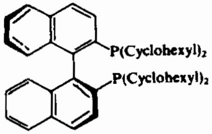
292: (−)-BINAPO (*159*)


P(C₆H₅)₂
P(C₆H₅)₂

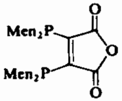
293: (*S*)-(−)-BINAP (45, 106, 158, 159, 258, 261, 272)


NH PPh₂
NH PPh₂

294: (*R*)-(+)-BDPAB (*117*)

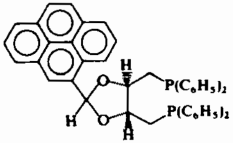

P(Cyclohexyl)₂
P(Cyclohexyl)₂

295: (+)-Cy-BINAP (158)

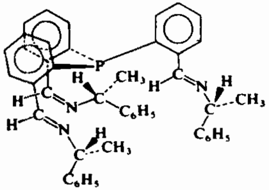

O
Men₂P
O
Men₂P
O

296: (1*R*, 3*R*, 4*S*)-(−) (*101*)

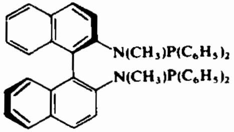
$C_{45}H_{36}$ · · ·


H
O
P(C₆H₅)₂
H
O
P(C₆H₅)₂
H

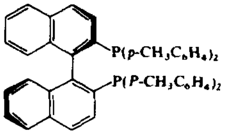
297: (*R*, *R*)-(−) (*114*)


P
H
CH₃
H
C
N
H
C₆H₅
H
C
N
H
CH₃
C
C₆H₅
H
C
N
H
C
CH₃
C₆H₅

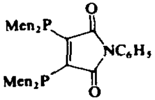
298: (*R*)-(+)-Trisiminphos (*122*)


N(CH₃)P(C₆H₅)₂
N(CH₃)P(C₆H₅)₂

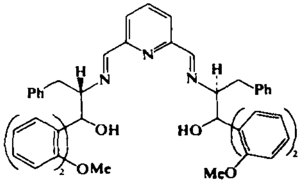
299: (*R*)-(−)-Me-BDPAB (*117*)


P(p-CH$_3$C$_6$H$_4$)$_2$
P(P-CH$_3$C$_6$H$_4$)$_2$

300: (+)-*p*-Tol-BINAP (158)

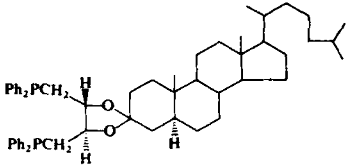

Men$_2$P
Men$_2$P
NC$_6$H$_5$

301: (1*R*, 3*R*, 4*S*)-(−) (*101*)

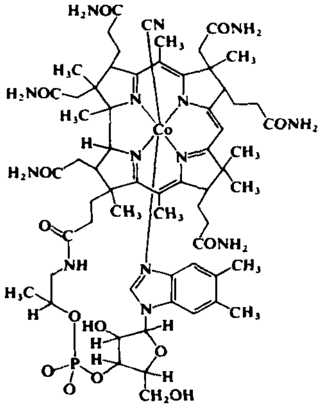

Ph
Ph
OMe
MeO
OH
HO

302: (*S*, *S*) (232)

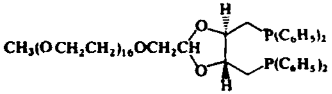
$C_{56}H_{72}$ · · ·


Ph$_2$PCH$_2$
Ph$_2$PCH$_2$

303: (−)-DIOCOL (228)

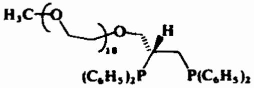

Co
CN
H$_2$NOC
CONH$_2$
CH$_2$OH
NH

304: Cob(I)alamin (234)

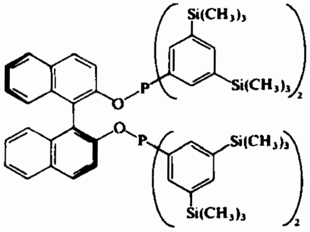

CH$_3$(OCH$_2$CH$_2$)$_{16}$OCH$_2$CH
P(C$_6$H$_5$)$_2$
P(C$_6$H$_5$)$_2$

305: (*R*, *R*)-(−)-PGE-17-Diop (*133*, *135*)

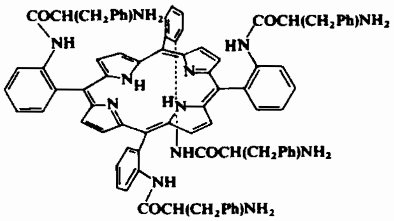
Table 2 (Contd)



306: D-(+) (*135*)

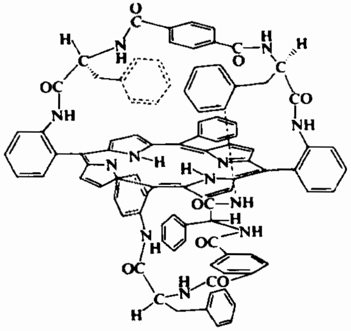


307: (*258*)

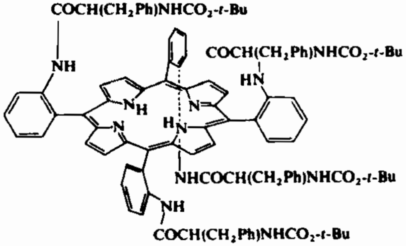


308: L (*295*)

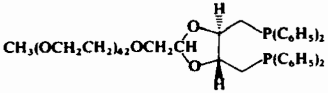
$C_{96}H_{72}$ · · ·



309: L (*295*)

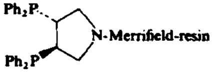


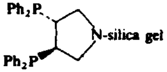
310: (*295*)

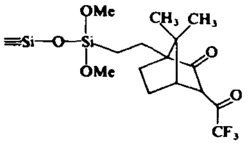


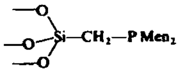
311: (*R*, *R*) (*135*)

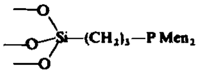
Polymeric Ligands

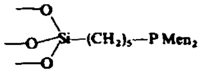

312: (*R*, *R*) (61)

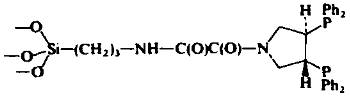

313: (*R*, *R*) (61)

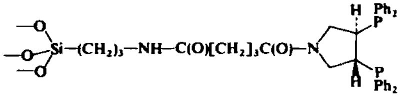

314: Silica-bonded trifluoroacetyl-(+)-camphor (*78*)

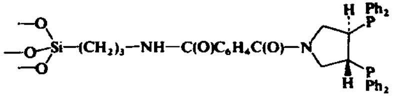

315: (1*R*, 3*R*, 4*S*)-(−) (*74*)

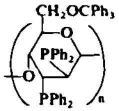

316: (1*R*, 3*R*, 4*S*)-(−) (*74*)

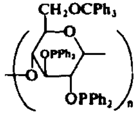

317: (1*R*, 3*R*, 4*S*)-(−) (*74*)


318: (3*R*, 4*R*) (*62*)


319: (3*R*, 4*R*) (*62*)


320: (3*R*, 4*R*) (*62*)


321: (*162*)


322: (*162*)

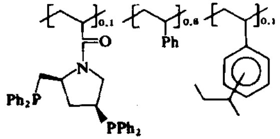

323: (2*S*, 4*S*) (*76*)

Table 2 (Contd)

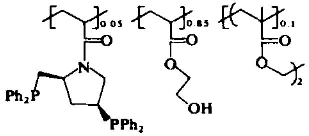
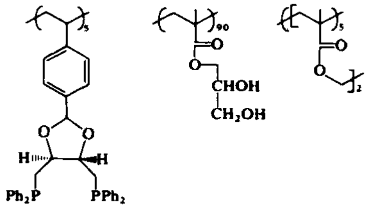
 **324**: (2*S*, 4*S*) (*76*)	 **325**: (*S*, *S*) (*75*)	Carbohydrate **326**: β-Cyclodextrin (299)
Protein	Protein	Protein
327: Bovine serum albumin (*314*)	**328**: Enoate reductase (157)	**329**: 2-Oxocarboxylate reductase (157)

Table 3

Optically Active Compounds Obtained by Enantioselective Catalysis with Transition Metal Complexes, Recorded in *CA Selects* "Catalysis (Organic Reactions)" Jan. 1, 1984 Through Oct. 20, 1986.

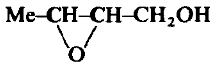
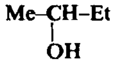
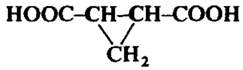
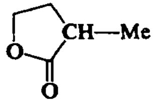
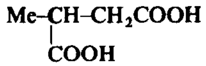
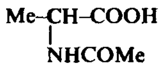
Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_4H_8O_2$		Ti(O-*i*-Pr)$_4$/**DET**	85, *S,S*	Epoxidation of *cis*-crotyl alcohol with *t*-BuOOH; Sharpless reaction	290
$C_4H_{10}O$	 $Me\text{-}\underset{OH}{CH}\text{-}Et$	Raney-Ni/**TA**/NaBr/pivalic acid	49, *S*	Hydrogenation of 2-butanone with H_2; high e.e. only on catalyst modification with carboxylic acids	186
		[Rh(nbd)**Chiraphos**] X/KOH; Prophos	3.4, *S*	Transfer hydrogenation of 2-butanone with *i*-PrOH	194
$C_5H_6O_4$		$CoCl_2$/Zn/**155**	2.4, *R,R*	Cyclopropanation of dimethyl fumarate with Zn/CH_2Br_2; substrate and chiral ligand of the same type	233
$C_5H_8O_2$		Ru_2Cl_4(**Diop**)$_3$	11.3, *S*	Hydrogenation of racemic 2-Me succinic anhydride with H_2; less e.e. for accompanying regioisomer	172
$C_5H_8O_4$	 $Me\text{-}\underset{COOH}{CH}\text{-}CH_2COOH$	[Rh(cod)Cl]$_2$/**224**; [Rh(cod)$_2$]BF_4	62, *R*	Hydrogenation of itaconic acid with H_2; new bisdiphenylphosphine ligand	113
		[Rh(cod)**243**]BF_4; **232**, **233**, **243″**	64, *S*	As above; new aminoalcohol derived chelate ligands; strong solvent dependence	98
		[Rh(cod) **271**]ClO_4; **272**, **290**	74, *S*	As above; water soluble catalysts containing solubilized PPM derivatives	134

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		[Rh(cod)**305**]ClO_4; **289**	39, *S*	As above; water soluble catalysts due to polyethylene glycol–Diop ligands	133
		[Rh(cod)**263**]ClO_4; **208**, **229**, **246**, **276**, **283**	20, *R*	As above; new polyethylene glycol–1,2-diphosphine ligands	127
		[Rh(cod) **311**]ClO_4	47, *S*	As above; polyethylene glycol–diphosphine ligands; e.e. higher in EtOH than in water	135
		[Rh(nbd)**146′**]ClO_4; **217′**, **277**	43, *S*	As above; new ferrocenylphosphine ligands with $P(t\text{-}Bu)_2$ groups	112
		$[Rh(cod)Cl]_2$/**294**; **299**	80, *S*	As above; new bisdiphenylphosphine derivative of 2,2′-diamino-1,1′-binaphthyl	117
		$[Rh(cod)_2]BF_4$/**228**; **240**, **241**	65, *R*	As above; electrostatic interaction of ligand NMe_2 with substrate COOH	153
		$[Rh(cod)_2]BF_4$/**228**; **240**, **241**, **261**, **262**	76, *R*	As above; electrostatic interaction substrate/ligand	119
		$[Rh(cod)Cl]_2$/**143**; $[Rh(cod)_2]BF_4$	68, *S*	As above; new diphenylphosphinite ligand derived from L-rhamnose	107
		$[Rh(C_8H_{14})_2Cl]_2$/**138**; **Diop**	69.6, *R*	As above; new PPh_2 ligands from glucose; ligand type/product configuration	128
		$[Rh(nbd)_2]BF_4$/**301**; **296**	9, *S*	As above; new dimenthylphosphine ligands	101

		[Rh(cod) **185**]BF$_4$	62, *R*	As above; less e.e. with Me fumaric acid than with itaconic acid	116
		[Rh(**Diop′**)$_2$]BF$_4$	56, *R*	As above; less e.e. with citraconic acid	111
		[Rh(C$_2$H$_4$)$_2$Cl]$_2$/**315**	83, *S*	As above; SiO$_2$-bound ligand; metal leaching	74
$C_5H_9NO_3$	 $Me-CH(NHCOMe)-COOH$	[Rh(**293**)]ClO$_4$	67, *R*	Hydrogenation of α-*N*-acetamidoacrylic acid with H$_2$	45
		Ru$_2$Cl$_4$(**Binap**)$_2$NEt$_3$	76, *S*	As above; Binap and *p*-tolyl-Binap ligands	106
		[Rh(nbd)**193**]ClO$_4$; **192**	90	As above; new ligand BDPP = 2,4-bis-diphenylphosphinopentane	65
		[Rh(nbd)**Diop**]BF$_4$;	77, *R*	As above; new Diop-derived ligands	114
		[Rh(nbd)**127**]PF$_6$; **125**	50, *S*	As above; new PP and AsAs ligands with chiral P and As atoms	118
		[Rh(nbd)**277**]ClO$_4$; **146′**, **166′**, **211′**	95, *R*	As above: new ferrocenylphosphine ligands with P(*t*-Bu)$_2$ groups	112
		[Rh(nbd)$_2$]ClO$_4$/Cu(**239**)Cl; **239**	89, *S*	As above; new L-threonine derived NPP ligand; X-ray structure of Cu complex	109
		[Rh(cod)**290**]ClO$_4$; **271**, **272**	57, *R*	As above; water soluble catalysts containing solubilized PPM derivatives	134
		[Rh(cod)**305**]ClO$_4$; **289**	43, *R*	As above; water soluble catalysts due to polyethylene glycol–Diop ligands	133
		[Rh(cod)**229**]ClO$_4$; **208**, **246**, **253**, **263**, **270**, **276**, **283**	81, *S*	As above; new polyethylene glycol–1,2-diphosphine ligands	127
		[Rh(cod)**306**]ClO$_4$; **311**	60, *S*	As above; for 1,4-diphosphines e.e. higher in EtOH than in water	135

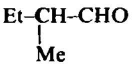
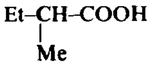
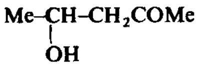
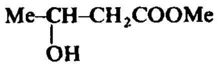
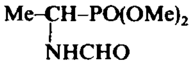
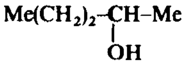
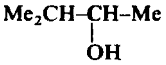
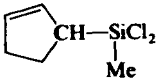
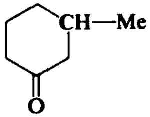
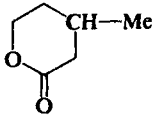
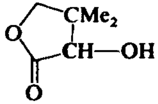
$C_5H_{10}O$	 $\mathrm{Et{-}CH(Me){-}CHO}$	**(Diop)**Pt($SnCl_3$)Cl	46.7, *R*	Hydroformylation of butene-1 and other butenes with CO/H_2	222
		(Chiraphos) Pt($SnCl_3$)Cl; **Diop**, other Pt, Rh catalysts	40, *S*	As above; isomerization and product configuration; mechanism	224
$C_5H_{10}O_2$	 $\mathrm{Et{-}CH(Me){-}COOH}$	**(Chiraphos)**Pt($SnCl_3$)Cl; **Diop**, other Pt, Rh catalysts	66, *R*	Hydrogenation of tiglic acid with H_2; phosphinite ligand from L-rhamnose	107
		$Ru_4(CO)_8$(malonate)$_2$/**Diop**; $Ru_2(CO)_4(7\text{-}H^+)_2(PPh_3)_2$	51.2, *S*	As above, similar e.e. with other carboxylic acids, *R*-, *S*-, *R*,*S*-2-Me-butanoic acid	156
		Pd/C/Zonyl-FCS/methyl viologen/**328**	>97, *R*	Hydrogenation of tiglinate with H_2 in phosphate buffer	157
		Ru_2Cl_4**(Diop)**$_3$	26.4, *R*	Transfer hydrogenation of (*E*)-α-methyl crotonic acid with PhCHOHMe; mechanism	196
	 $\mathrm{Me{-}CH(OH){-}CH_2COMe}$	Raney-Cu/**24**; **6**, **9**	1.4	Hydrogenation of acetylacetone with H_2; correlation e.e./CD of model complexes	178
$C_5H_{10}O_3$	 $\mathrm{Me{-}CH(OH){-}CH_2COOMe}$	Raney-Ni/**TA**/NaBr treated with pyridine and amines	83	Hydrogenation of Me acetoacetate with H_2; durable heterogeneous catalyst	69
		Ni/SiO_2/**TA**; Ni-**tartrate**, Na_2[Ni-**tartrate**]	35	As above; liquid-phase and gas-phase reactions; dual-site hydrogenation mechanism	181
		Ni/SiO_2/**TA**	45	As above; gas-phase reaction; surface studies	184
		Ni/SiO_2/modified with TA	60, *R*	As above; influence of alkali halide addition	179 180

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		Raney-Ni/**6**; **1**, **2**, **4**, **5**, **9**, **12**, **25**	14.2	As above; correlation of e.e. with CD of model complexes	178
$C_5H_{12}NO_4P$	 $\mathrm{Me{-}\underset{NHCHO}{CH}{-}PO(OMe)_2}$	[Rh(nbd)Cl]$_2$/**Diop**′	76, L	Hydrogenation of *N*-formyl-dehydro-amino-phosphonic acid with H_2	155
$C_5H_{12}O$	 $\mathrm{Me(CH_2)_2{-}\underset{OH}{CH}{-}Me}$	Raney-Ni/**TA**/NaBr/pivalic acid	63, *S*	Hydrogenation of 2-pentanone with H_2; modified heterogeneous catalyst	186
	 $\mathrm{Me_2CH{-}\underset{OH}{CH}{-}Me}$	Raney-Ni/**TA**/NaBr/pivalic acid	63, *S*	Hydrogenation of 3-Me-2-butanone with H_2; modified heterogeneous catalyst	186
$C_6H_{10}Cl_2Si$		$PdCl_2$/**166**	25, *S*	Hydrosilylation of cyclopentadiene with $HSiMeCl_2$; followed by ethanolysis	216
$C_6H_{10}O$		$Co_2(CO)_6$(**NMDPP**)$_2$	1.4, *S*	Hydrogenation of 3-Me-2-cyclopentenone with H_2	161
$C_6H_{10}O_2$		Ru_2Cl_4(**Binap**)$_2NEt_3$	39, *R*	Hydrogenation of 3-Me-glutaric anhydride with H_2	106
$C_6H_{10}O_3$		[Rh(C_8H_{14})$_2$Cl]$_2$/**247**; **264**, **265**	66, *S*	Hydrogenation of α-keto pantoyl lactone with H_2; peralkyldiphosphine ligands	166

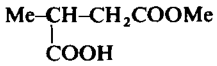
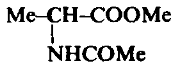
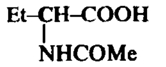
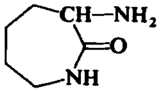
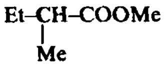
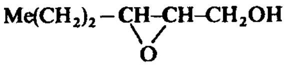
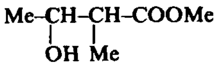
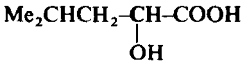
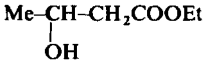
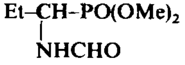
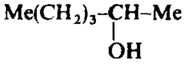
		[Rh(cod)Cl]$_2$/**220**	45, *R*	As above; cyclohexyl derivatives of Diop and Chiraphos as ligands	165
		[Rh(cod)Cl]$_2$/**BPPM**	84, *R*	As above; *Org. Synth.* procedure	169
$C_6H_{10}O_4$	 $Me\text{-}CH(COOH)\text{-}CH_2COOMe$	[Rh(C_8H_{14})$_2$Cl]$_2$/**138**; **Diop**	89.7, *R*	Hydrogenation of Me itaconate with H_2; ligand type/product configuration	128
$C_6H_{11}NO_3$	 $Me\text{-}CH(NHCOMe)\text{-}COOMe$	Co(dmgH)$_2$/PPh$_3$/**167**; **99**, **99″**, **135**, **135″**, **167″**	43.4, *R*	Hydrogenation of Me α-*N*-acetamidoacrylate with H_2; mechanism	138
		[Rh(cod)Cl]$_2$/**Prophos**; **Norphos**, **Diop′**, **BPPFA**	76.5, *S*	As above; attempted e.e. calculation with Ruch–Ugi model	121
	 $Et\text{-}CH(NHCOMe)\text{-}COOH$	[Rh(cod)Cl]$_2$/**Norphos**; **Prophos**, **Diop**, **275**	91.4, *S*	Hydrogenation of (*Z*)-α-*N*-acetamidocrotonic acid with H_2	125
$C_6H_{12}N_2O$		PdCl$_2$/**19**	11, *S*	Hydrogenation of 3-nitrocaprolactam with H_2; L-lysine on hydrolysis	307
$C_6H_{12}O_2$	 $Et\text{-}CH(Me)\text{-}COOMe$	CoCl$_2$/**Diop**/NEt$_3$	4.5, *S*	Hydrogenation of methyl α-methylcrotonate with H_2	136
		CoCl$_2$/**Diop**/NEt$_3$	10, *R*	Transfer hydrogenation of methyl α-methylcrotonate with PhCHOHMe	196
		Ti(O-*i*-Pr)$_4$/**DET**	96.8, *S,S*	Epoxidation of (*E*)-2-hexen-1-ol with *t*-BuOOH; *Org. Synth.* procedure	291
$C_6H_{12}O_3$	 $Me\text{-}CH(OH)\text{-}CH(Me)\text{-}COOMe$	Raney-Ni modified with TA	60, *S*	Hydrogenation of Me 2-Me-3-oxo-butyrate with H_2; crystallization involved; step in sawfly pheromone synthesis	185

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		[Rh(nbd)$_2$]BF$_4$/**Dipamp**; **Chiraphos**	95	Hydrogenation of Me α-(1-hydroxyethyl)-acrylate with H_2; kinetic resolution	160
$C_6H_{12}O_3$	 $\mathrm{Me_2CHCH_2{-}\underset{OH}{\underset{\vert}{C}}H{-}COOH}$	Pd/C/Zonyl-FCS/methylviologen/**329**	>95	Hydrogenation of 1-oxo-3-methylpentanoic acid with H_2	157
	 $\mathrm{Me{-}\underset{OH}{\underset{\vert}{C}}H{-}CH_2COOEt}$	Cu/Ru on aerosil, modified with **TA**	25, *R*	Hydrogenation of ethyl acetoacetate with H_2; Cu/Ru synergism within catalyst	183 173
		Ni modified with **TA**	71, *R*	As above; new heterogeneous catalyst by $Ni(NO_3)_2$ decomposition	174
		Cu/Pd modified with **TA**	9, *R*	As above; skeletal Cu/Pd catalyst	175
		$LnNi_{5-x}Cu_xH_n$ modified with **TA**; Ln = La, Sm, Gd	17, *R*	As above; intermetallic hydrides as heterogeneous catalysts	176
		Cu/Ni modified with **TA**	50	As above; unsupported Cu/Ni catalysts obtained by precipitation	177
		Raney-Cu/**12**; **1**, **5**, **6**, **9**, **11**, **14**, **24**, **25**, **37**, Raney-Co	10.8	As above; correlation of e.e. with CD of model complexes	178
		Cu/Ni modified with **TA**; **24**	22	As above; rate and e.e. dependent on pH of modifying solution	182
$C_6H_{14}NO_4P$	 $\mathrm{Et{-}\underset{NHCHO}{\underset{\vert}{C}}H{-}PO(OMe)_2}$	[Rh(nbd)Cl]$_2$/**Diop**′	64, *R*	Hydrogenation of *N*-formyl-dehydroaminophosphonic acid with H_2	155
$C_6H_{14}O$	 $\mathrm{Me(CH_2)_3{-}\underset{OH}{\underset{\vert}{C}}H{-}Me}$	Raney-Ni/**TA**/NaBr/pivalic acid; other additives	66, *S*	Hydrogenation of 2-hexanone with H_2; modified heterogeneous catalyst	186

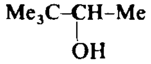
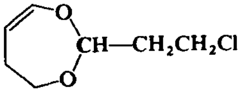
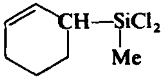
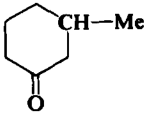
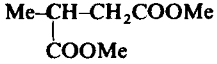
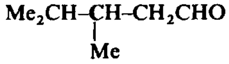
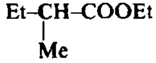
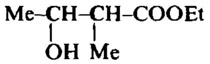
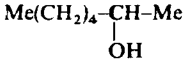
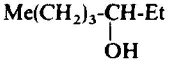
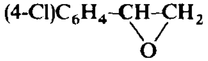
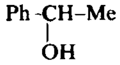
	 $Me_3C\text{-}CH(OH)\text{-}Me$	Raney-Ni/**TA**/NaBr/pivalic acid	74, *S*	Hydrogenation of methyl *t*-butyl ketone with H_2; modified heterogeneous catalyst	186
		[Rh(nbd)**Chiraphos**]$^+$/ KOH; **Prophos**	9.4, *R*	Transfer hydrogenation of methyl *t*-butyl ketone with *i*-PrOH	194
$C_7H_{11}ClO_2$		[Rh(cod)Cl]$_2$/**Diop**/NaBH$_4$; Ru$_2$Cl$_4$(**Diop**)$_3$	12.1	Isomerization of 2-(*β*-chlorethyl)-4,7-dihydro-1,3-dioxepine	273
$C_7H_{12}Cl_2Si$		PdCl$_2$/**166**	>1, *S*	Hydrosilylation of cyclohexadiene-1,3 with HSiMeCl$_2$; ethanolysis	216
$C_7H_{12}O$		Co$_2$(CO)$_6$(**NMDPP**)$_2$	10, *S*	Hydrogenation of 3-Me-2-cyclohexenone with H_2; less e.e. for 2-Me-isomer	161 168
$C_7H_{12}O_4$	 $Me\text{-}CH(COOMe)\text{-}CH_2COOMe$	[Rh(C_8H_{14})$_2$Cl]$_2$/**138**; **Diop**	6.4, *R*	Hydrogenation of dimethyl itaconate with H_2; new PPh$_2$ ligand from glucose	128
$C_7H_{14}O$	 $Me_2CH\text{-}CH(Me)\text{-}CH_2CHO$	[Rh(nbd)Cl$_2$/**Chiraphos**; **Diop**, other Rh, Pt catalysts	21.8, *R*	Hydroformylation of 2,3-dimethyl-1-butene with CO/H_2	224
$C_7H_{14}O_2$	 $Et\text{-}CH(Me)\text{-}COOEt$	CoCl$_2$/**Diop**/NEt$_3$	11.7, R	Hydrogenation of ethyl α-methylcrotonate with H_2	136
		PdCl$_2$(PhCN)$_2$/**212**	43, *R*	Hydrocarboalkoxylation of *cis*-2-butene/EtOH with CO; less e.e. with other butenes	227
		Ru$_2$Cl$_4$(**Diop**)$_3$	9.8, *R*	Transfer hydrogenation of ethyl α-methylcrotonate with PhCHOHMe	196

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_7H_{14}O_3$	 $\mathrm{Me{-}\underset{OH}{CH}{-}\underset{Me}{CH}{-}COOEt}$	$[Rh(nbd)_2]BF_4$/**Dipamp**; **Chiraphos**, **Diop**	60, *R*	Hydrogenation of Et α-(1-hydroxyethyl)-acrylate; kinetic resolution	160
$C_7H_{16}O$	 $\mathrm{Me(CH_2)_4{-}\underset{OH}{CH}{-}Me}$	$[Rh(nbd)_2]BF_4$/**Dipamp**; **Chiraphos**, **Diop**	66, *S*	Hydrogenation of 2-heptanone with H_2; modified heterogeneous catalyst	186
		$[Ir(cod)Cl]_2$/**192**/NaOMe	3.4, *R*	Transfer hydrogenation of heptanone-2 with *i*-PrOH	66
	 $\mathrm{Me(CH_2)_3{-}\underset{OH}{CH}{-}Et}$	$[Ir(cod)Cl]_2$/**192**/NaOMe	4.2, *R*	Transfer hydrogenation of heptanone-3 with *i*-PrOH	66
C_8H_7ClO	 $\mathrm{(4\text{-}Cl)C_6H_4{-}CH{-}CH_2}$ (epoxide, O bridging)	Basket handle-Fe-porphyrin **309**; porphyrins **308**, **310**	50, *R*	Epoxidation of *p*-chlorostyrene with iodosylbenzene	295
$C_8H_{10}O$	 $\mathrm{Ph{-}\underset{OH}{CH}{-}Me}$	$[Rh(nbd)Cl]_2$/**193**; **192**	82, *S*	Hydrogenation of acetophenone with H_2; new bisdiphenylphosphine ligand BDPP	65
		$[Ir(C_8H_{14})_2Cl]_2/P(OMe)_3$/**28**, **17**	12, *S*	As above; mandelic acid derived ligands	167
		$Co_2(CO)_6$(**53**)$_2$; **152**	2, *S*	As above; menthyl–PMe_2 ligand	168
		Ir(cod)acac/**145″**/KOH; **53**, **168**, other Ir catalysts	47.8, *R*	Transfer hydrogenation of acetophenone with *i*-PrOH	191
		$[Rh(cod)Cl]_2$/**119**/KOH; **68**, **69**, **70**, **112**	14.8, *R*	As above; new bipyridyl and phenanthroline based ligands	192

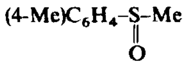
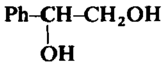
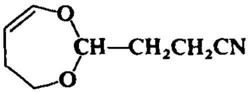
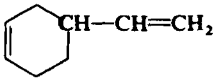
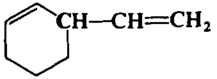
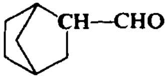
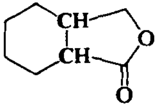
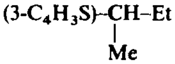
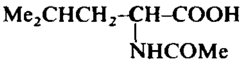
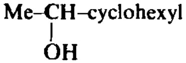
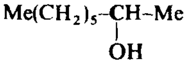
		[Rh(**Chiraphos**)]$_3$(OMe)$_2$ PF$_6$/KOH; **Prophos**, other Rh catalysts	24.9, *R*	As above; change of procatalyst during activation process	193
		[Ir(cod) **Prophos**]$^+$/KOH; **Chiraphos**, **Diop**, Rh catalysts	58, *S*	As above; catalyst activation and product configuration	194
		[Ir(cod)Cl]$_2$/**192**/NaOMe; **193**, **278**, Rh complexes	18, *R*	As above; phosphinite better than phosphine ligands; catalyst activation	66
$C_8H_{10}OS$	 $(4\text{-Me})C_6H_4\text{-}\underset{\underset{O}{\|}}{S}\text{-Me}$	MoO(O$_2$)$_2$/**DET**	22.3	Oxidation of methyl *p*-tolyl sulfide with *t*-BuOOH; stoichiometric examples	287
		Ti(O-*i*-Pr)$_4$/H$_2$O/**DET**	83	As above; nonlinearity of optical induction and e.e. of chiral auxiliary	292
$C_8H_{10}O_2$	 $Ph\text{-}\underset{\underset{OH}{\|}}{CH}\text{-}CH_2OH$	OsO$_4$/**327**	61, *S*	*cis*-Dihydroxylation of styrene with *t*-BuOOH	314
$C_8H_{11}NO_2$		Ru$_2$Cl$_4$(**Diop**)$_3$/NaBH$_4$; [Rh(cod)Cl]$_2$/**Diop**	25.4	Isomerization of 2-(*β*-cyanethyl)-4,7-dihydro-1,3-dioxepine	273
C_8H_{12}		FeCl$_2$/**144**/reduction; **101**, **110**	62, *S*	Dimerization of butadiene; additionally 1,5-cod and oligomers	279
		FeCl$_2$/EtMgI/**128**; **153**	16, *S*	As above; NN ligands of imine type	278
		Ni^0/**187**	15	As above; new aminophosphine–phosphinite ligands from aminoalcohols	103
		Ni(cod)$_2$/AlEt$_2$Cl/**286**; **244**, **291**	93, *S*	Hydrovinylation of cyclohexa-1,3-diene with ethylene	277

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_8H_{12}O$		(**Diop**)Pt(SnCl$_3$)Cl; **Chiraphos**, other Pt, Rh catalysts	29.2, *R*	Hydroformylation of norbornene with CO/H$_2$; transition state model to explain enantioselectivity	224
$C_8H_{12}O_2$		RhH(**Diop**)$_2$	29, *R*, *S*	Dehydrogenation of 1,2-bis-(hydroxymethyl)cyclohexane	313
$C_8H_{12}S$	 $(3\text{-}C_4H_3S)\text{-}\underset{\mid \atop Me}{CH}\text{-}Et$	NiCl$_2$/**Prophos**	2, *S*	Cross-coupling of *sec*-Bu Grignard with 3-Br-thiophene	244
$C_8H_{15}NO_3$	 $Me_2CHCH_2\text{-}\underset{\mid \atop NHCOMe}{CH}\text{-}COOH$	[Rh(nbd)**127**]PF$_6$/NEt$_3$; **125**	94, *S*	Hydrogenation of (*Z*)-α-*N*-acetyl-dehydroleucine; new PP and AsAs ligands	118
		[Rh(nbd)$_2$]ClO$_4$/**239**; Cu(**239**)Cl	89, *S*	As above; new L-threonine derived NPP ligand; X-ray structure of Cu complex	109
		[Ir(cod)PhCN(**NMDPP**)]ClO$_4$	6.7	As above; alkyl-substituted dehydro-amino acid	147
$C_8H_{16}O$	 $Me\text{-}\underset{\mid \atop OH}{CH}\text{-}cyclohexyl$	[Ir(cod)**Prophos**]$^+$/KOH; **Chiraphos**, Rh catalysts	17, *S*	Transfer hydrogenation of methyl cyclohexyl ketone with *i*-PrOH	194
$C_8H_{18}O$	 $Me(CH_2)_5\text{-}\underset{\mid \atop OH}{CH}\text{-}Me$	Raney-Ni/TA/NaBr/pivalic acid; other additives	66, *S*	Hydrogenation of 2-octanone with H$_2$; modified heterogeneous catalysts	186

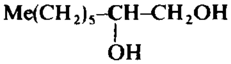
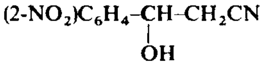
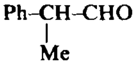
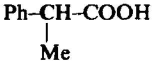
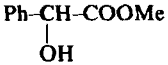
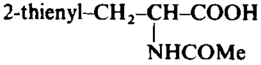
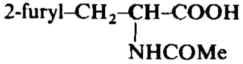
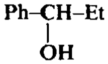
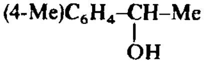
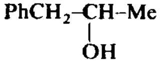
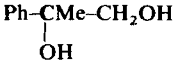
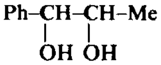
$C_8H_{18}O_2$	 $\mathrm{Me(CH_2)_5{-}\underset{\underset{OH}{\mid}}{CH}{-}CH_2OH}$	Raney-Ni/**TA**/NaBr/ pivalic acid; other additives	9, *S*	*cis*-Dihydroxylation of oct-1-ene with *t*-BuOOH	314
$C_9H_8N_2O_3$	 $\mathrm{(2\text{-}NO_2)C_6H_4{-}\underset{\underset{OH}{\mid}}{CH}{-}CH_2CN}$	$PdCl_2(PhCN)_2$/**Diop**; **BPPM**	34	Aldol condensation of $2\text{-}NO_2$-benzaldehyde with cyanomethyl $SnMe_3$; same e.e. with 3-isomer	302
$C_9H_{10}O$	 $\mathrm{Ph{-}\underset{\underset{Me}{\mid}}{CH}{-}CHO}$	Rh/**243**"	25	Hydroformylation of styrene with CO/H_2	103
		$PtCl_2/SnCl_2$/**BPPM**; polymer catalyst containing **323**, **324**	80, *S*	As above; highest e.e. reported for a polymer catalyst	76
		(**Chiraphos**)$Pt(SnCl_3)Cl$; **Diop**, other Rh, Pt catalysts	45, *R*	As above; model for the transition state to explain enantioselectivity	224
$C_9H_{10}O_2$	 $\mathrm{Ph{-}\underset{\underset{Me}{\mid}}{CH}{-}COOH}$	[Rh(**Diop'**)$_2$]BF_4	41, *R*	Hydrogenation of α-phenyl acrylic acid with H_2; mechanism	111
		[Rh(cod)**185**]BF_4/ $H_2NCHMePh$	18, *R*	As above; ligand Dioxop; e.e. increases on amine addition	116
		$[Rh(cod)Cl]_2$/polymer attached **Diop**	56, *R*	As above; polymer contains pendant alcohol groups	75
$C_9H_{10}O_3$	 $\mathrm{Ph{-}\underset{\underset{OH}{\mid}}{CH}{-}COOMe}$	Eu(**47**-H^+)$_3$; Eu(**63**-H^+)$_3$	55, *S*	Transfer hydrogenation of Me phenyl glyoxylate with dihydropyridines	195
		$[Rh(cod)Cl]_2$/**220**	21, *R*	Hydrogenation of methyl phenylglyoxylate with H_2	165

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_9H_{11}NO_3S$	 $\text{2-thienyl-CH}_2\text{-}\underset{\text{NHCOMe}}{\text{CH}}\text{-COOH}$	[Rh(cod)**Diop**]ClO_4; [Rh(cod)Cl]$_2$/**Diop**	72	As above; cationic catalyst gives higher e.e. than neutral catalyst	145
$C_9H_{11}NO_4$	 $\text{2-furyl-CH}_2\text{-}\underset{\text{NHCOMe}}{\text{CH}}\text{-COOH}$	[Rh(cod)Cl]$_2$/**Diop**	9	Hydrogenation of the corresponding dehydroamino acid with H_2	145
$C_9H_{12}O$	 $\text{Ph-}\underset{\text{OH}}{\text{CH}}\text{-Et}$	Ir(cod)acac/**168**/KOH	35.1, *S*	Transfer hydrogenation of propiophenone with *i*-PrOH	191
		[Ir(cod)**Prophos**]$^+$/KOH; **Chiraphos**, Rh catalysts	66, *S*	As above; catalyst activation and product configuration	194
		[Ir(cod)Cl]$_2$/**192**/NaOMe	10.9, *R*	As above; phosphinite ligands better than phosphine ligands	66
	 $\text{(4-Me)C}_6\text{H}_4\text{-}\underset{\text{OH}}{\text{CH}}\text{-Me}$	[Ir(cod)Cl]$_2$/**192**/NaOMe	4.1, *S*	Transfer hydrogenation of 4-methylacetophenone with *i*-PrOH	66
	 $\text{PhCH}_2\text{-}\underset{\text{OH}}{\text{CH}}\text{-Me}$	[Rh(nbd)**Chiraphos**]$^+$/ KOH; **Prophos**	12.9, *S*	Transfer hydrogenation of methyl benzyl ketone with *i*-PrOH	194
$C_9H_{12}O_2$	 $\text{Ph-}\underset{\text{OH}}{\text{CMe}}\text{-CH}_2\text{OH}$	OsO_4/**327**	68, *S*	*cis*-Dihydroxylation of α-methylstyrene with *t*-BuOOH	314
	 $\text{Ph-}\underset{\text{OH}}{\text{CH}}\text{-}\underset{\text{OH}}{\text{CH}}\text{-Me}$	OsO_4/**327**	18, *S*, *S*	*cis*-Dihydroxylation of trans-β-methylstyrene with *t*-BuOOH	314

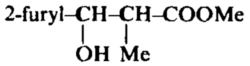
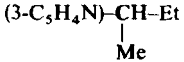
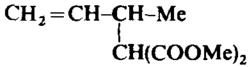
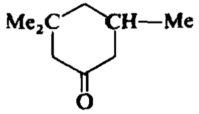
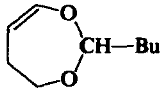
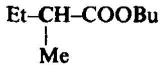
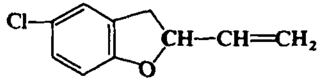
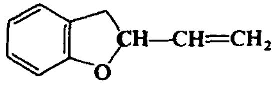
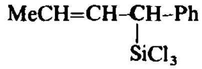
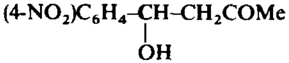
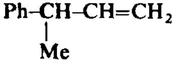
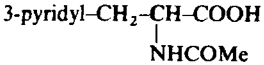
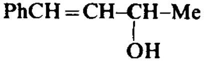
$C_9H_{12}O_4$	 $\text{2-furyl-}\underset{\text{OH}}{\text{CH}}\text{-}\underset{\text{Me}}{\text{CH}}\text{-COOMe}$	$[Rh(nbd)_2]BF_4$/**Dipamp**	81	Hydrogenation of the corresponding methylacrylate; kinetic resolution	160
$C_9H_{13}N$	 $(3\text{-}C_5H_4N)\text{-}\underset{\text{Me}}{\text{CH}}\text{-Et}$	$NiCl_2$/**Prophos**	16.4, *S*	Cross-coupling of *sec*-Bu Grignard with pyridyl halide; less e.e. with 2-,4-isomers	244
$C_9H_{14}O_4$	 $CH_2{=}CH\text{-}\underset{CH(COOMe)_2}{CH}\text{-Me}$	(η^3-Butenyl)Pt(**Dipamp**); **Diop**, **252**, Pd catalysts	23, *S*	Allylic alkylation of but-2-enyl acetate with $NaCH(COOMe)_2$; mechanism	256
$C_9H_{16}O$		$Co_2(CO)_6$(**NMDPP**)$_2$; **53**, **152**	16, *S*	Hydrogenation of isophorone with H_2	161
$C_9H_{16}O_2$		Ru_2Cl_4(**Diop**)$_3$	13.9	Isomerization of 2-*n*-butyl-4,7-dihydro-1,3-dioxepine	273
$C_9H_{18}O_2$	 $\text{Et-}\underset{\text{Me}}{\text{CH}}\text{-COOBu}$	$CoCl_2$/**Diop**/NEt_3	6.3, *R*	Hydrogenation of *n*-butyl α-methylcrotonate with H_2	136
$C_{10}H_9ClO$		[(**35**-H^+)PdOAc]$_2$	7.4, *S*	Cyclization of 4-Cl-2-(2-butenyl)phenol with *t*-BuOOH or $Cu(OAc)_2/O_2$	312
$C_{10}H_{10}O$		[(**35**-H^+)PdOAc]$_2$; [(**97**-H^+)PdOAc]$_2$	18, *S*	Cyclization of 2-(2-butenyl)phenol with *t*-BuOOH or $Cu(OAc)_2/O_2$	312
$C_{10}H_{11}Cl_3Si$	 $MeCH{=}CH\text{-}\underset{SiCl_3}{CH}\text{-Ph}$	$PdCl_2$/**166**	64, *S*	Hydrosilylation of 1-Ph-butadiene with $HSiCl_3$; regioisomer; ethanolysis	215

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{10}H_{11}NO_3$	$\mathrm{Me{-}\underset{\underset{\displaystyle NHCOPh}{|}}{C}H{-}COOH}$	[Rh(**Binap**)]ClO_4	98, *R*	Hydrogenation of α-*N*-benzamidoacrylic acid with H_2	45
$C_{10}H_{11}NO_4$	 $\mathrm{(4\text{-}NO_2)C_6H_4{-}\underset{\underset{\displaystyle OH}{|}}{C}H{-}CH_2COMe}$	$Zn(NO_3)_2 \cdot 6H_2O$/**56**; **8**, **10**, **19**, **32**, **43**, **45**	[α] −30°	Aldol condensation of 4-NO_2-benzaldehyde with acetone; 16 mol% catalyst; presence of β-cyclodextrin	300 298 299
$C_{10}H_{12}$	 $\mathrm{Ph{-}\underset{\underset{\displaystyle Me}{|}}{C}H{-}CH{=}CH_2}$	$NiCl_2$/**75**; **15**, **27**, **61**, **74**	16.9, *S*	Cross-coupling of 1-phenylethyl Grignard with vinyl bromide; new S,N ligands	238
		$NiCl_2$/**122**; **114**, **120**, **131**, **132**, **194**	65, *S*	As above; P,N ligands derived from sulfur containing amino acids	240
		Ni^{2+}/**103**; **173**, **181**, **196**, **210**	46, *R*	As above; new macrocyclic ligands with sulfide and amine binding sites	239
		$NiCl_2$/**160**; **156**, **157**, **161**, **164**, **165**, **267**, **273**	31.9, *R*	As above; NN, PN, and PP ligands; correlation of e.e. and conformation	241
$C_{10}H_{12}N_2O_3$	 $\mathrm{3\text{-}pyridyl{-}CH_2{-}\underset{\underset{\displaystyle NHCOMe}{|}}{C}H{-}COOH}$	$[Rh(cod)Cl]_2$/**Diop**; other Rh catalysts	35	Hydrogenation of the corresponding dehydroamino acid with H_2	145
$C_{10}H_{12}O$	$\mathrm{Ph{-}\underset{\underset{\displaystyle Me}{|}}{C}H{-}CH_2CHO}$	$[Rh(nbd)Cl]_2$/**Chiraphos**; **Diop**, other Rh, Pt catalysts	21.4, *S*	Hydroformylation of 2-phenylpropene with CO/H_2	224
	 $\mathrm{PhCH{=}CH{-}\underset{\underset{\displaystyle OH}{|}}{C}H{-}Me}$	$[Ir(cod)(OMe)_2]_2$/**105**	7.4, *S*	Hydrogenation of the keto group in benzylideneacetone with H_2	170

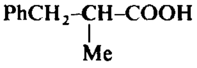
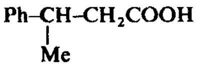
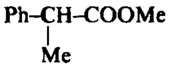
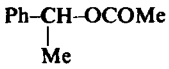
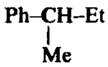
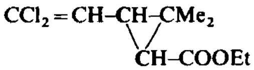
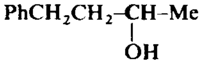
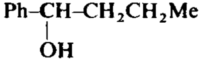
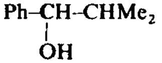
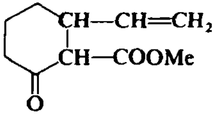
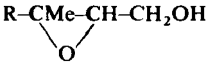
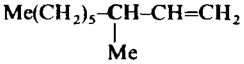
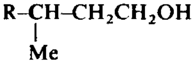
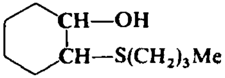
$C_{10}H_{12}O_2$	 $PhCH_2\text{-}CH(Me)\text{-}COOH$	[Rh(cod)Cl]$_2$/**294**; other catalysts	49, *R*	Hydrogenation of α-methylcinnamic acid with H_2	117
		[Rh(cod)**185**]BF$_4$/ $H_2NCHMePh$	59, *S*	As above; ligand Dioxop; influence of temperature, H_2-pressure	116
		[Rh(nbd)**277**]ClO$_4$; **211′**	61, *R*	As above; new ferrocenylphosphine ligands with P(*t*-Bu)$_2$ groups	112
		Modified Pd/C/**328**	>97	As above; Zonyl-FCS, methylviologen in phosphate buffer	157
	 $Ph\text{-}CH(Me)\text{-}CH_2COOH$	[Rh(cod)**185**]BF$_4$/ $H_2NCHMePh$	24, *R*	Hydrogenation of β-methylcinnamic acid with H_2; ligand Dioxop	116
	 $Ph\text{-}CH(Me)\text{-}COOMe$	PdCl$_2$(PhCN)$_2$/**212**	22, *S*	Hydrocarboalkoxylation of styrene/ MeOH with CO; additionally linear isomer	116
	 $Ph\text{-}CH(Me)\text{-}OCOMe$	[Rh(cod)**243**]PF$_6$; **243″**	24, *R*	Hydrogenation of acetyl α-phenylvinyl alcohol	98
$C_{10}H_{14}$	 $Ph\text{-}CH(Me)\text{-}Et$	NiCl$_2$/**Norphos**; **Chiraphos**, **Prophos**, **Dipamp**, **222**, **226**	50.7, *R*	Cross-coupling of *s*-Bu Grignard with phenylhalides	244
		[Rh(cod)Cl]$_2$/**322**; **321**	30, *R*	Hydrogenation of α-ethylstyrene with H_2	162
		[Rh(nbd)Cl]$_2$/**193**; **192**	54, *S*	As above; new diphosphine ligand BDPP	65
		$H_4Ru_4(CO)_8$(**Diop**)$_2$	9, *S*	As above; influence of isomerization on e.e.	163
		[Rh(cod)Cl]$_2$/**294**; other catalysts	2.4, *S*	As above; new diphosphine ligand derived from 2,2′-diamino-1,1′-binaphthyl	117
$C_{10}H_{14}Cl_2O_2$	 $CCl_2{=}CH\text{-}\overline{CH\text{-}CMe_2}\text{-}CH\text{-}COOEt$	[Cu(**234**)$_2$]Cl$_2$; **180**, **191**, **203**	28, *S*, *R*	Cyclopropanation of the corresponding olefin with ethyl diazoacetate	232

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{10}H_{14}O$	 $PhCH_2CH_2\text{-}CH(OH)\text{-}Me$	Raney-Ni/TA/NaBr/ pivalic acid	58, *S*	Hydrogenation of 1-Ph-3-butanone with H_2; modified heterogeneous catalyst	186
	 $Ph\text{-}CH(OH)\text{-}CH_2CH_2Me$	$[Ir(cod)$**Prophos**$]^+$/KOH; **Chiraphos**, Rh catalysts	56, *S*	Transfer hydrogenation of *n*-butyrophenone with *i*-PrOH	194
		$[Ir(cod)Cl]_2$/**192**/NaOMe	1, *S*	As above; BDPOP ligand	66
	 $Ph\text{-}CH(OH)\text{-}CHMe_2$	$[Ir(cod)$**Prophos**$]^+$/KOH; **Chiraphos**, Rh catalysts	51, *S*	Transfer hydrogenation of *i*-butyrophenone with *i*-PrOH; catalyst activation	194
$C_{10}H_{14}O_3$		$Pd(OAc)_2$/**BPPFA′**	32, *R*	Cyclization of Me 3-oxo-7-MeOOCO-8-nonenoate; less e.e. with isomer	257
$C_{10}H_{18}O_2$	 $R\text{-}CMe\text{-}CH\text{-}CH_2OH$	$Ti(O\text{-}i\text{-}Pr)_4$/**DET**	91, *S*, *S*	Epoxidation of geraniol ($R = Me_2C{=}CH\text{-}(CH_2)_2$) with *t*-BuOOH; Sharpless reaction	290
$C_{10}H_{20}$	 $Me(CH_2)_5\text{-}CH(Me)\text{-}CH{=}CH_2$	$NiCl_2$/**132**; **114**, **122**, **131**	18, *S*	Cross-coupling of 2-octyl Grignard with vinyl bromide	240
$C_{10}H_{20}O$	 $R\text{-}CH(Me)\text{-}CH_2CH_2OH$	$[Rh(cod)Cl]_2$/**295**; **300**, **Chiraphos**, **Diop′**, **Binap′**	66, *S*	Hydrogenation of nerol ($R = Me_2C{=}CH\text{-}(CH_2)_2$) with H_2; less e.e. with geraniol	158
$C_{10}H_{20}OS$		Zn(TA-2H$^+$); heterogeneous system	85	Ring-opening of cyclohexene oxide with *n*-BuSH	72

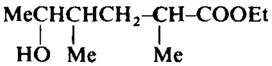
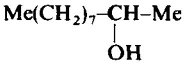
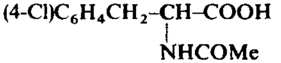
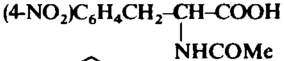
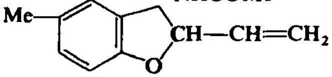
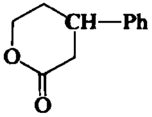
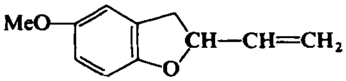
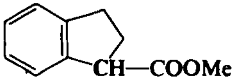
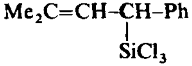
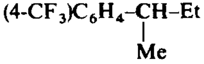
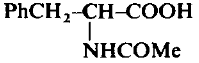
$C_{10}H_{20}O_3$	 $\mathrm{MeCH(OH)CH(Me)CH_2{-}CH(Me){-}COOEt}$	[Rh(**Binap**')]$^+$	96, *S*	Hydrogenation of homoallylic alcohol with H_2; OH-directed 1,3-stereocontrol	159
$C_{10}H_{22}O$	 $\mathrm{Me(CH_2)_7{-}CH(OH){-}Me}$	Raney-Ni/TA/NaBr/ pivalic acid	58, *S*	Hydrogenation of 2-decanone with H_2; modified heterogeneous catalyst	186
$C_{11}H_{12}ClNO_3$	 $\mathrm{(4\text{-}Cl)C_6H_4CH_2{-}CH(NHCOMe){-}COOH}$	[Rh(cod)**Diop**]ClO_4; other Rh catalysts	72	Hydrogenation of 4-Cl-substituted acetamidocinnamic acid with H_2	129
$C_{11}H_{12}N_2O_5$	 $\mathrm{(4\text{-}NO_2)C_6H_4CH_2{-}CH(NHCOMe){-}COOH}$	$[Rh(cod)Cl]_2$/**Diop**; other Rh catalysts	68	Hydrogenation of 4-NO_2 substituted acetamidocinnamic acid with H_2	129
$C_{11}H_{12}O$		[(**35**-H$^+$)PdOAc]$_2$	21, *S*	Cyclization of 4-Me-2-(2-butenyl)phenol with $Cu(OAc)_2/O_2$ or *t*-BuOOH	312
$C_{11}H_{12}O_2$		Ru_2Cl_4(**Binap**)$_2NEt_3$	33, *R*	Hydrogenation of 3-phenyl-glutaric anhydride with H_2	**106**
		[(**35**-H$^+$)PdOAc]$_2$	26, *S*	Cyclization of 4-MeO-2-(2-butenyl)phenol with $Cu(OAc)_2/O_2$ or *t*-BuOOH	312
		$PdCl_2(PhCN)_2$/**212**	5	Hydrocarboalkoxylation of indene/ MeOH with CO; additionally regio-isomer	227
$C_{11}H_{13}Cl_3Si$	 $\mathrm{Me_2C{=}CH{-}CH(SiCl_3){-}Ph}$	$PdCl_2$(**166**)	50, *S*	Hydrosilylation of 1-Ph-3-Me-butadiene/ $HSiCl_3$; less e.e. for 2-, 4-Me isomers	215
$C_{11}H_{13}F_3$	 $\mathrm{(4\text{-}CF_3)C_6H_4{-}CH(Me){-}Et}$	$NiCl_2$/**Prophos**	36, *R*	Cross-coupling of *sec*-Bu Grignard with 4-CF_3-phenyl bromide	244

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{11}H_{13}NO_3$	 $PhCH_2\text{-}CH(NHCOMe)\text{-}COOH$	[Rh(**Binap**)]ClO_4	84, *R*	Hydrogenation of (*Z*)-α-*N*-acetamidocinnamic acid with H_2	45
		[Rh(nbd)**260**]PF_6; **268**, **268″**	69, *R*	As above; new proline derived PNNP ligands	99
		$[Rh(nbd)_2]BF_4$/**296**; **301**, [Rh(nbd)**296**]BF_4	69.7	As above; new chelating dimenthylphosphine ligands	101
		$[Rh(cod)Cl]_2$/**175**; **198**	88, *R*	As above; catalysis in an aqueous–organic two-phase system	132
		[Rh(cod)**271**]ClO_4; **272**	87, *R*	As above; water soluble catalysts containing solubilized PPM derivatives	134
		[Rh(cod)**305**]ClO_4; **289**	69, *R*	As above; water soluble catalysts from polyethylene glycol–Diop ligands	133
		[Rh(cod)**208**]ClO_4; **229**, **246**, **253**, **263**, **270**, **276**, **283**	86, *S*	As above; new polyethylene glycol–1,2-diphosphine ligands	127
		[Rh(cod)**Dipamp**]ClO_4; **Norphos**, **Diop**, **205**, **311**	98	As above; for 1,4-diphosphines e.e. higher in EtOH than in water	135
		[Rh(cod)**207**]$(BF_4)_2$	90, *S*	As above; water soluble catalyst; solvent MeOH for free acid, water for Na salt	63
		[Rh(cod)**244**]ClO_4; $[Rh(cod)Cl]_2$/**244**, **243″**	51, *R*	As above; new PP ligands derived from aminoalcohols	102
		[Rh(cod)**248**]BF_4; **249**, **254**, **257**, **258**, **312**, **313**	99, *S*	As above; new effective diphosphine ligand benzoylpyrphos and derivatives	61

[Rh(hexadiene-1.5)Cl]$_2$/**98**; **65**, **84**, **85**	22, *R*	As above; new PN and AsN chelate ligands	104
[Rh(nbd)$_2$]BF$_4$/Na salt of **206**; **188**	30, *S*	As above; amino acid derived ligands $(Ph_2PCH_2)_2N$–CHR–COONa	105
Ru$_2$Cl$_4$(**Binap**)$_2$NEt$_3$	86, *S*	As above; Binap catalyst modified with NEt$_3$	106
[Rh(cod)Cl]$_2$/**143**/NEt$_3$	48, *R*	As above; new diphenylphosphinite ligand derived from L-rhamnose	107
[Rh(nbd)$_2$]ClO$_4$/Cu(**239**)Cl; **239**	89, *R*	As above; new L-threonine derived NPP ligand; X-ray structure of Cu complex	109
[Rh(nbd)Cl]$_2$/[Cu(**278**)Cl]$_n$	94, *R*	As above; new bisdiphenylphosphinite ligand; efficient in enamide hydrogenation	110
[Rh(**Diop**)$_2$]BF$_4$	94, *S*	As above; kinetic measurements; mechanism	111
[Rh(nbd)**277**]ClO$_4$; **146**′ **166**′, **211**′	91, *S*	As above; new ferrocenylphosphine ligands with P(*t*-Bu)$_2$ groups	112
[Rh(cod)Cl]$_2$/**BPPM** on acetate modified charcoal	86.5, *R*	As above; heterogeneous catalyst superior to homogeneous system	70
[Rh(cod)Cl]$_2$/**224**; [Rh(cod)$_2$]BF$_4$	55, *S*	As above; new bisdiphenylphosphine ligand	113
[Rh(nbd)**281**]BF$_4$; **Diop**, **237**, **238**, **280**	88, *R*	As above; new Diop derived ligands	114
[Rh(cod)Cl]$_2$/**325**′, polymeric system	77, *S*	As above; small effects of *R*, *S*, or racemic alcohol groups pendant in the polymer	75

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		[Rh(cod)$_2$BF$_4$/**240**; **228**, **241**	29, *S*	As above; electrostatic interaction of ligand NMe$_2$ with substrate COOH	153
		[Rh(nbd)**193**]ClO$_4$; **192**, other Rh catalysts	96, *R*	As above; new ligand BDPP = 2,4-bisdiphenylphosphinopentane	65
		[Rh(nbd)Cl]$_2$/**201**; [Rh(nbd)$_2$]BF$_4$	58, *S*	As above; new D-mannitol derived ligand	115
		[Rh(cod)**185**]BF$_4$	90, *S*	As above; ligand Dioxop; influence of temperature, H$_2$-pressure, amine addition	116
		[Rh(cod)**294**]BF$_4$; **299**, other catalysts	91, *R*	As above; new bisdiphenylphosphine derivative of 2,2′-diamino-1,1′-binaphthyl	117
		[Rh(nbd)**125**]PF$_6$/NEt$_3$; **127**, other catalysts	80, *S*	As above; new PP and AsAs ligands with chiral P and As atoms	118
		[Rh(cod)$_2$]BF$_4$/**240**; **228**, **241**, **261**, **262**	29, *S*	As above; ^{31}P NMR and CD data; several Rh species present in solution	119
		[Rh(cod)**Diop′**]ClO$_4$	98.5	As above; crystallization involved	120
		[Rh(cod)Cl]$_2$/**Norphos**; **Prophos**, **Diop′**, **BPPFA**	94.6, *S*	As above; attempted e.e. calculation with Ruch–Ugi model	121
		[Rh(cod)**Diop**]ClO$_4$; other Rh catalysts	87	As above; isolated cationic catalyst better than *in situ* neutral catalyst	129
		[Rh(cod)Cl]$_2$/**170**; **172**, **298**, other Rh catalysts	17, *S*	As above; new PN and PNNN ligands with optically active *N* substituents	122

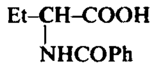
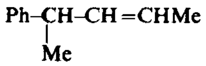
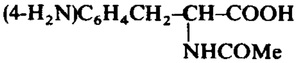
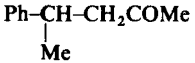
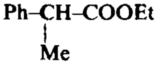
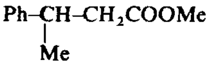
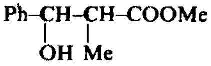
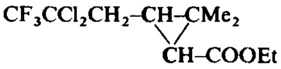
	$Rh_6(CO)_{10}$(**Diop**)$_3$	20, *R*	As above; cluster catalysis/fragment catalysis	131
	Rh(cod)(**118**-H^+)/**Norphos**	95, *S*	As above; no effect of ligand **118** on e.e.	123
	[Rh(cod)Cl]$_2$/**275**	94, *R*	As above; one P atom of (−)-Diop blocked by the $C_5H_5Mn(CO)_2$ fragment	124
	[Rh(cod)**243**]BF_4; **232**, **233**, **243″**	80, *R*	As above; new aminoalcohol derived chelate ligands; strong solvent dependence	98
	[Rh(cod)**244**]ClO_4	94, *R*	As above; new aminophosphine phosphinite ligand; e.e. increase with H_2-pressure	126
	[Rh(C_8H_{14})$_2$Cl]$_2$/**138**; **Diop**, **142**	91.6, *S*	As above; new PPh_2 ligands from glucose; ligand type/product configuration	128
	[Rh(C_2H_4)$_2$Cl]$_2$/**187**	86.5	As above; phosphinite aminophosphine ligand/product configuration	130
	[Rh(cod)$_2$]BF_4/**319**; **318**, **320**	97	As above; best polymer catalyst described	62
	[Rh(C_2H_4)$_2$Cl]$_2$/**317**; **174**, **221**, **315**, **316**	87, *R*	As above; e.e. of SiO_2-bound catalyst higher than of homogeneous analog	74
	[Rh(cod)Cl]$_2$/**Norphos**; **BPPFA**, **Prophos**, **Diop**	67, *S*	Transfer hydrogenation of (*Z*)-α-*N*-acetamidocinnamic acid with HCOOH	197
 $Et-\underset{NHCOPh}{CH}-COOH$	[Rh(cod)Cl]$_2$/**Prophos**; **Norphos**, **Diop**, **275**	54.8, *S*	Hydrogenation of (*E*)-α-benzamidocrotonic acid with H_2, less e.e. with (*Z*)-isomer	125

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		$[\mathrm{Rh(cod)Cl}]_2$/**Norphos**, **BPPFA′**, **Prophos**, **Diop**	47.1, *S*	Transfer hydrogenation of Me (*Z*)-α-*N*-benzamidocrotonate with HCOOH, ester hydrolysis; less e.e. with (*E*)-isomer	197
$C_{11}H_{14}$	 $\mathrm{Ph{-}\underset{Me}{CH}{-}CH{=}CHMe}$	$\mathrm{NiCl_2}$/**Chiraphos**	47, *R*	Cross-coupling of phenyl Grignard with substituted allylic ester	264
		$\mathrm{Pd(dba)_2}$/**168**; **NMDPP**, **Diop**	12, *S*	Coupling of pent-3-en-2-acetate with PhZnCl, mechanism	265
$C_{11}H_{14}N_2O_3$	 $\mathrm{(4\text{-}H_2N)C_6H_4CH_2{-}\underset{NHCOMe}{CH}{-}COOH}$	[Rh(cod)**Diop**]$\mathrm{ClO_4}$; other Rh catalysts	66	Hydrogenation of 4-NH_2-substituted acetamidocinnamic acid with H_2	129
$C_{11}H_{14}O$	 $\mathrm{Ph{-}\underset{Me}{CH}{-}CH_2COMe}$	$\mathrm{Co_2(CO)_6}$(**NMDPP**)$_2$	2	Hydrogenation of 4-phenyl-3-penten-2-one with H_2	161
$C_{11}H_{14}O_2$	 $\mathrm{Ph{-}\underset{Me}{CH}{-}COOEt}$	$\mathrm{PdCl_2(PhCN)_2}$/**212**	16, *S*	Hydrocarboalkoxylation of styrene/EtOH with CO; additionally linear isomer	227
	 $\mathrm{Ph{-}\underset{Me}{CH}{-}CH_2COOMe}$	$\mathrm{PdCl_2(PhCN)_2}$/**212**	48.2, *S*	Hydrocarboalkoxylation of 2-Ph-propene/MeOH with CO; less e.e. with 1-Ph-propene	227
$C_{11}H_{14}O_3$	 $\mathrm{Ph{-}\underset{OH}{CH}{-}\underset{Me}{CH}{-}COOMe}$	$[\mathrm{Rh(nbd)_2}]\mathrm{BF_4}$/**Dipamp**	89	Hydrogenation of Me α-(hydroxybenzyl)-acrylate with H_2; kinetic resolution	160
$C_{11}H_{15}Cl_2F_3O_2$		$\mathrm{Cu(\mathbf{191})_2Cl_2}$; **180**, **203**, **234**, **302**	38, *S*,*S*	Cyclopropanation of olefin with diazo acetate; additionally *cis* isomer	232

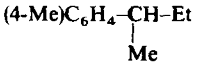
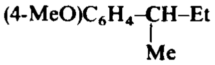
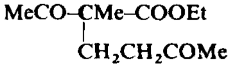
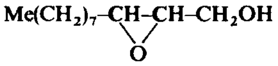
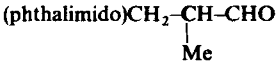
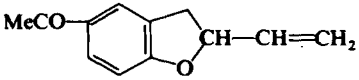
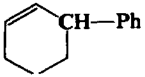
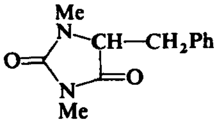
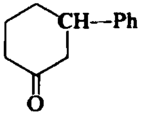
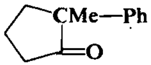
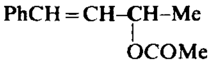
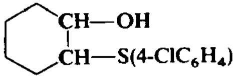
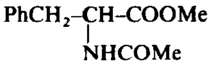
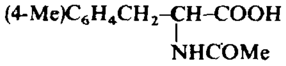
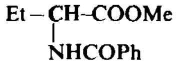
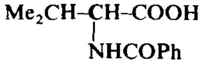
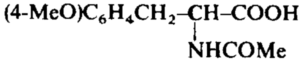
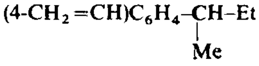
$C_{11}H_{16}$	 $(4\text{-Me})C_6H_4\text{-}\underset{\substack{\vert\\ Me}}{C}H\text{-Et}$	$NiCl_2$/**Prophos**	36, *R*	Cross-coupling of *sec*-Bu Grignard with 4-tolyl bromide; less e.e. for 2-isomer	244
$C_{11}H_{16}O$	 $(4\text{-MeO})C_6H_4\text{-}\underset{\substack{\vert\\ Me}}{C}H\text{-Et}$	$NiCl_2$/**Prophos**	[α] −10°	Cross-coupling of *sec*-Bu Grignard with 4-MeO-phenyl bromide	244
$C_{11}H_{18}O_4$	 $MeCO\text{-}\underset{\substack{\vert\\ CH_2CH_2COMe}}{C}Me\text{-}COOEt$	$Co(acac)_2$/**67**	4.5, *S*	Michael addition of Et α-methylacetoacetate with vinyl methyl ketone	305
$C_{11}H_{22}O_2$		$Ti(O\text{-}i\text{-}Pr)_4$/**DET**	>95, *S*,*S*	Epoxidation of (*E*)-2-undecen-1-ol with *t*-BuOOH; two crystallizations	290
$C_{12}H_{11}NO_3$	 $(\text{phthalimido})CH_2\text{-}\underset{\substack{\vert\\ Me}}{C}H\text{-}CHO$	$RhH(CO)(PPh_3)_3$/**303**; **Diop**	1.5, *R*	Hydroformylation of (*E*)-*N*-propenylphthalimide with CO/H_2; linear isomer	228
$C_{12}H_{12}O_2$		$[(\mathbf{35}\text{-}H^+)PdOAc]_2$	1.1, *S*	Cyclization of 4-acetyl-2-(2-butenyl)-phenol with $Cu(OAc)_2/O_2$ or *t*-BuOOH	312
$C_{12}H_{14}$		$Pd(dba)_2$/**NMDPP**; **Chiraphos**	9.4, *S*	Coupling of cyclohex-2-en-1-acetate with PhZnCl; mechanism	265
$C_{12}H_{14}N_2O_2$		$Co(dmgH)_2/PPh_3$/**99**″; **121**, **121**″, **129**, **135**, **135**″, **167**	79.1, *S*	Hydrogenation of *N*,*N*′-dimethyl-5-benzylidenehydantoin with H_2; mechanism	138
$C_{12}H_{14}O$		$Co_2(CO)_6(\mathbf{NMDPP})_2$	(−)	Hydrogenation of 3-phenyl-2-cyclohexenone with H_2	161

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		[Rh(**Chiraphos**)$_2$]Cl	69, *S*	Intramolecular hydroacylation of 2-Ph-2-Me-pent-4-enal; kinetic resolution	303 304
$C_{12}H_{14}O_2$	 $PhCH{=}CH\text{-}\underset{\displaystyle OCOMe}{CH}\text{-}Me$	[η^3-C_3H_5)PdCl]$_2$/**285**	$k_{S/R}$ 1.2	Allylic alkylation of 1-styrylethyl acetate/ NaCH(COMe)$_2$; kinetic resolution	260
$C_{12}H_{15}ClOS$		Zn(TA-2H$^+$), heterogeneous system	65	Ring-opening of cyclohexene oxide with 4-ClC$_6$H$_4$-SH	72
$C_{12}H_{15}NO_3$	 $PhCH_2\text{-}\underset{\displaystyle NHCOMe}{CH}\text{-}COOMe$	CoCl$_2$/**NMDPP**/NaBH$_4$; Co (**13**-H$^+$)/PPh$_3$/NaBH$_4$	60, *S*	Hydrogenation of Me (*Z*)-α-*N*-acetamidocinnamate with H$_2$	137
		[Rh(cod)**243**]BF$_4$; **175**, **232**, **233**, **243**″	75, *R*	As above; new aminoalcohol derived chelate ligands; strong solvent dependence	98
		[Rh(cod)Cl]$_2$/**301**; [Rh(nbd)$_2$] BF$_4$/**296**	56, *R*	As above; new chelating dimenthyl-phosphine ligands	101
		[Rh(cod)Cl]$_2$/**175**; **198**	86, *R*	As above; catalysis in an aqueous–organic two-phase system	132
		[Rd(cod)**305**]ClO$_4$; **289**	69, *R*	As above; water soluble catalysts from polyethylene glycol–Diop ligands	133
		[Rh(cod)**283**]ClO$_4$; **208**, **229**, **246**, **253**, **263**, **270**, **276**	84, *S*	As above; new polyethylene glycol–1,2-diphosphines	127
		[Rh(cod)**305**]ClO$_4$; **311**	60	As above; e.e. higher in EtOH than in water	135

$[Rh(nbd)_2]BF_4$/**206**; **188**, **189**, **202**, **215**, **217**, **227**, **250**	34.7, *S*	As above; new amino acid derived ligands $(Ph_2PCH_2)_2N–CHR–COONa$	105
$[Rh(nbd)Cl]_2$/$[Cu($**278**$)Cl]_n$; **192**	79, *R*	As above; new bis-diphenylphosphinite ligand; efficient in enamide hydrogenation	110
$[Rh(nbd)$**Diop**$]BF_4$; **237**, **238**, **280**, **281**	85, *R*	As above; new Diop derived ligands	114
$[Rh(nbd)$**193**$]ClO_4$; **192**, other Rh catalysts	72	As above; new ligand BDPP = 2,4-bisdiphenylphosphinopentane	65
$[Rh(nbd)Cl]_2$/**201**; $[Rh(nbd)_2]BF_4$	43, *S*	As above; new D-mannitol derived ligand	115
$[Rh(cod)$**185**$]BF_4$	90, *S*	As above; ligand Dioxop; influence of temperature, H_2-pressure, amine addition	116
$[Rh(C_8H_{14})_2Cl]_2$/**294**	69, *R*	As above; new bisdiphenylphosphine derivative of 2,2′-diamino-1,1′-binaphthyl	117
$[Rh(nbd)$**127**$]PF_6$; **125**	51, *S*	As above; new PP and AsAs ligands; spectroscopy of intermediates; mechanism	118
$[Rh(cod)_2]BF_4$; **240**	35, *R*	As above; slow reaction of NMe_2 catalyst	119
$[Rh(cod)acac]/Ph_2P(CH_2)_4–PPh_2$/**38**, other phosphines	10.8	As above; kinetic measurements with related systems	120
$Rh_4(CO)_{10}$**Diop**/**Diop**; **Chiraphos**, other Rh catalysts	65, *R*	As above; cluster catalysis/fragment catalysis	131
$[Rh(cod)Cl]_2$/**Prophos**; **Norphos**, **Diop′**, **BPPFA**	94.7, *S*	As above; attempted e.e. calculation with Ruch–Ugi model	121

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		[Rh(cod)$_2$]BF$_4$/**320**	100	As above; best polymer catalyst described	62
		[Rh(cod)**207**](BF$_4$)$_2$	96, *S*	As above; highly active and stable catalyst	63
		[Rh(C$_2$H$_4$)$_2$Cl]$_2$/**316**	9, *R*	As above; SiO$_2$-bound ligand; metal leaching	74
		[Rh(C$_8$H$_{14}$)$_2$Cl]$_2$/**138**	70.6, *S*	As above; new PPh$_2$ ligand from glucose; ligand type/product configuration	128
	 $\text{(4-Me)C}_6\text{H}_4\text{CH}_2\text{–}\underset{\text{NHCOMe}}{\underset{\vert}{\text{CH}}}\text{–COOH}$	[Rh(cod)**Diop**]ClO$_4$; other Rh catalysts	71	Hydrogenation of 4-Me acetamidocinnamic acid with H$_2$	129
	 $\text{Et–}\underset{\text{NHCOPh}}{\underset{\vert}{\text{CH}}}\text{–COOMe}$	[Rh(cod)Cl]$_2$/**Norphos**; **Prophos**, **Chiraphos**, **BPPFA**, **Diop**, **275**	70.9, *S*	Hydrogenation of Me (*Z*)-α-benzamidocrotonate with H$_2$; less e.e. with (*E*)-isomer	125
		[Rh(nbd)**127**]PF$_6$/NEt$_3$; **125**	79, *S*	As above; new PP and AsAs ligands with chiral P and As atoms	118
	 $\text{Me}_2\text{CH–}\underset{\text{NHCOPh}}{\underset{\vert}{\text{CH}}}\text{–COOH}$	[Rh(nbd)**125**]PF$_6$; **127**	89, *S*	Hydrogenation of 3-Me-α-benzamidobut-2-enoic acid with H$_2$	118
$C_{12}H_{15}NO_4$	 $\text{(4-MeO)C}_6\text{H}_4\text{CH}_2\text{–}\underset{\text{NHCOMe}}{\underset{\vert}{\text{CH}}}\text{–COOH}$	[Rh(cod)Cl]$_2$/**Diop**; other Rh catalysts	76	Hydrogenation of 4-MeO acetamidocinnamic acid with H$_2$	129
$C_{12}H_{16}$	 $\text{(4-CH}_2\text{=CH)C}_6\text{H}_4\text{–}\underset{\text{Me}}{\underset{\vert}{\text{CH}}}\text{–Et}$	NiCl$_2$/**Prophos**	36, *R*	Cross-coupling of *s*-Bu Grignard with 4-vinylphenyl bromide	244

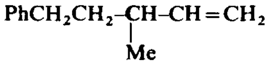
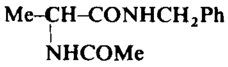
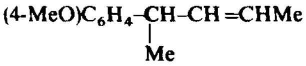
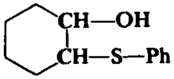
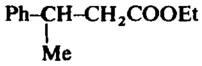
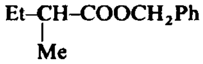
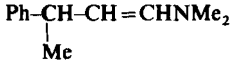
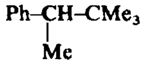
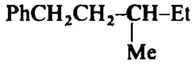
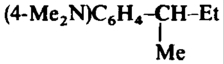
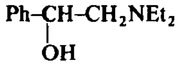
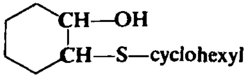
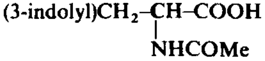
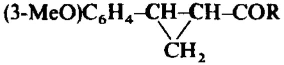
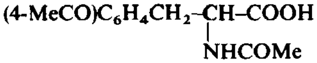
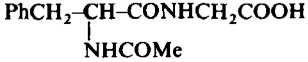
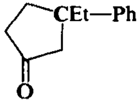
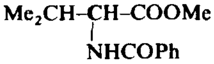
	 $\mathrm{PhCH_2CH_2{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}CH{=}CH_2}$	$H_4Ru_4(CO)_8$(**Diop**)$_2$	0.5, *S*	Isomerization of (*E*/*Z*)-3-methyl-5-phenylpent-2-ene	274
$C_{12}H_{16}N_2O_2$	 $\mathrm{Me{-}\underset{\displaystyle NHCOMe}{\underset{|}{C}}H{-}CONHCH_2Ph}$	[Rh(nbd)Cl]$_2$/**Dipamp**; **Diop'**	92, *S*	Hydrogenation of α-acetamidoacrylic acid *N*-benzyl amide with H_2	100
$C_{12}H_{16}O$	 $\mathrm{(4\text{-}MeO)C_6H_4{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}CH{=}CHMe}$	$NiCl_2$/**Chiraphos**	68, *R*	Cross-coupling of 4-methoxyphenyl Grignard with allylic ester	264
$C_{12}H_{16}OS$		Zn(**TA**-2H$^+$), heterogeneous system	61	Ring-opening of cyclohexene oxide with PhSH	72
$C_{12}H_{16}O_2$	 $\mathrm{Ph{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}CH_2COOEt}$	$PdCl_2(PhCN)_2$/**212**	31.5, *S*	Hydrocarboalkoxylation of 2-Ph-propene/EtOH with CO; additionally regioisomer	227
	 $\mathrm{Et{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}COOCH_2Ph}$	Ru_2Cl_4(**Diop**)$_3$	8.4, *R*	Transfer hydrogenation of benzyl (*E*)-α-Me-crotonate with PhCHOHMe; mechanism	196
$C_{12}H_{17}N$	 $\mathrm{Ph{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}CH{=}CHNMe_2}$	[Rh(cod)**Binap'**]ClO_4	90, *R*	Isomerization of (*E*)-*N*,*N*-dimethyl-3-phenyl-2-butenylamine	271
$C_{12}H_{18}$	 $\mathrm{Ph{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}CMe_3}$	$H_4Ru_4(CO)_8$(**Diop**)$_2$	9.7, *R*	Hydrogenation of 2-phenyl-3,3-dimethyl but-1-ene with H_2	163
	 $\mathrm{PhCH_2CH_2{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}Et}$	$H_4Ru_4(CO)_8$(**Diop**)$_2$	1.1, *S*	Hydrogenation of (*E*/*Z*)-3-methyl-5-phenylpent-2- ene with H_2	274
$C_{12}H_{19}N$	 $\mathrm{(4\text{-}Me_2N)C_6H_4{-}\underset{\displaystyle Me}{\underset{|}{C}}H{-}Et}$	$NiCl_2$(**Prophos**)	35.4, *R*	Cross-coupling of *s*-Bu Grignard with 4-NMe_2-phenyl bromide	244
$C_{12}H_{19}NO$	 $\mathrm{Ph{-}\underset{\displaystyle OH}{\underset{|}{C}}H{-}CH_2NEt_2}$	[Ir(cod)Cl]$_2$/**192**/NaOMe	26	Transfer hydrogenation of ω-NEt_2-acetophenone with *i*-PrOH	66

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{12}H_{22}OS$		Zn(TA-2H$^+$), heterogeneous system	79	Ring-opening of cyclohexene oxide with cyclohexanethiol	72
$C_{13}H_{14}N_2O_3$	 $\text{(3-indolyl)CH}_2\text{–CH(NHCOMe)–COOH}$	[Rh(cod)Cl]$_2$/**Diop**	86	Hydrogenation of the corresponding dehydroamino acid with H_2	145
$C_{13}H_{15}BrO_2$	 $\text{(3-MeO)C}_6\text{H}_4\text{–CH–CH–COR}$ (cyclo-CH_2)	Cu(TA-2H$^+$); Co(**36**-H$^+$)$_2$	46	Cyclopropanation of 3-MeO-styrene with 4-Br-1-diazo-2-butanone (R = CH_2CH_2Br)	71
$C_{13}H_{15}NO_4$	 $\text{(4-MeCO)C}_6\text{H}_4\text{CH}_2\text{–CH(NHCOMe)–COOH}$	[Rh(nbd)$_2$]ClO$_4$/**239**; Cu(**239**)Cl	84, *S*	Hydrogenation of the corresponding dehydroamino acid with H_2	109
$C_{13}H_{16}N_2O_4$	 $\text{PhCH}_2\text{–CH(NHCOMe)–CONHCH}_2\text{COOH}$	[Rh(cod)$_2$]BF$_4$/**240**; **228**, **241**	48, *S*	Hydrogenation of Ac-ΔPhe-Gly-OH with H_2	153
		[Rh(cod)$_2$]BF$_4$/**228**; **240**, **241**, **261**, **262**	48, *S*	As above; electrostatic interaction substrate/ligand; model	119
$C_{13}H_{16}O$		[Rh(**Chiraphos**)$_2$]Cl	[α] −2°	Intramolecular hydroacylation of substituted pent-4-enal; kinetic resolution	303 304
$C_{13}H_{17}NO_3$	 $\text{Me}_2\text{CH–CH(NHCOPh)–COOMe}$	[Ir(cod)PhCN(**NMDPP**)]ClO$_4$	4	Hydrogenation of tetrasubstituted enamide with H_2	147

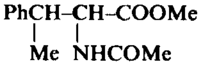
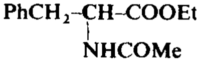
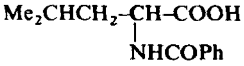
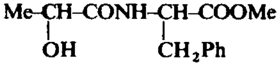
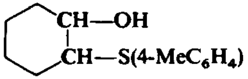
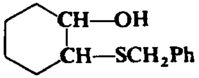
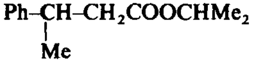
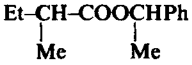
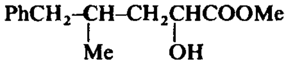
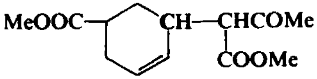
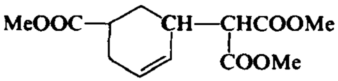
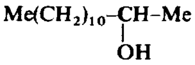
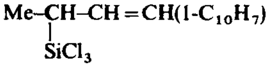
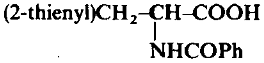
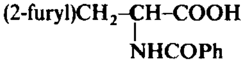
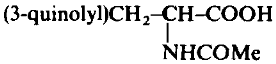
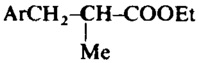
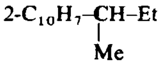
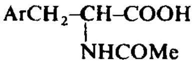
	 $\underset{Me}{PhCH}-\underset{NHCOMe}{CH}-COOMe$	$[Ir(cod)PhCN(\textbf{NMDPP})]ClO_4$	27	Hydrogenation of tetrasubstituted (Z)-enamide with H_2	147
	 $PhCH_2-\underset{NHCOMe}{CH}-COOEt$	$Rh_6(CO)_{10}(\textbf{Diop})_3$	34, *R*	Hydrogenation of Et α-*N*-acetamidocinnamate with H_2	131
	 $Me_2CHCH_2-\underset{NHCOPh}{CH}-COOH$	$[Rh(nbd)\textbf{127}]PF_6/NEt_3$; **125**	90, *S*	Hydrogenation of (*Z*)-α-*N*-benzoyl dehydroleucine with H_2	118
$C_{13}H_{17}NO_4$	 $Me-\underset{OH}{CH}-CONH-\underset{CH_2Ph}{CH}-COOMe$	$[Rh(cod)Cl]_2$/**BPPM**; **Diop**, **256**	28, *S*	Hydrogenation of Me (2-oxopropionyl) phenylalanine with H_2	154
$C_{13}H_{18}OS$		Zn(TA-2H$^+$), heterogeneous system	68	Ring-opening of cyclohexene oxide with 4-MeC_6H_4-SH, less e.e. with 2-, 3-isomers	72
		Zn(TA-2H$^+$), heterogeneous system	77	Ring-opening of cyclohexene oxide with $PhCH_2SH$	72
$C_{13}H_{18}O_2$	 $Ph-\underset{Me}{CH}-CH_2COOCHMe_2$	$PdCl_2(PhCN)_2$/**212**; **Diop**, **199**, **200**, **204**, **205**	52.8, *S*	Hydrocarboalkoxylation of 2-Ph-propene/*i*-PrOH with CO; optimization	227
	 $Et-\underset{Me}{CH}-COO\underset{Me}{CH}Ph$	$Ru_2Cl_4(\textbf{Diop})_3$	0.8, *S*	Transfer hydrogenation of phenethyl (*E*)-α-Me-crotonate with PhCHOHMe; mechanism	196
$C_{13}H_{18}O_3$	 $PhCH_2-\underset{Me}{CH}-CH_2\underset{OH}{CH}COOMe$	$[Rh(\textbf{Binap}')]^+$	60, *S*	Hydrogenation of homoallylic alcohol with H_2; OH-directed 1,3-stereocontrol; less e.e. for stereoisomer	159
$C_{13}H_{18}O_5$		$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**282**	71, *R*	Allylic alkylation of substituted allyl acetate with NaCH(COMe)COOMe	259

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{13}H_{18}O_6$		$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**282**	72, *R*	Allylic alkylation of substituted allyl acetate with $NaCH(COOMe)_2$	259
$C_{13}H_{28}O$	 $Me(CH_2)_{10}\text{-}\underset{\displaystyle OH}{\underset{\vert}{C}}H\text{-}Me$	Raney-Ni/TA/NaBr/pivalic acid	65, *S*	Hydrogenation of 2-tridecanone with H_2; modified heterogeneous catalyst	186
$C_{14}H_{13}Cl_3Si$	 $Me\text{-}\underset{\displaystyle SiCl_3}{\underset{\vert}{C}}H\text{-}CH{=}CH(1\text{-}C_{10}H_7)$	$PdCl_2$/**166**	55, *R*	Hydrosilylation of 1-Np-butadiene/$HSiCl_3$; ethanolysis	215
$C_{14}H_{13}NO_3S$	 $(2\text{-thienyl})CH_2\text{-}\underset{\displaystyle NHCOPh}{\underset{\vert}{C}}H\text{-}COOH$	[Rh(cod)**Diop**]ClO_4; $[Rh(cod)Cl]_2$/**Diop**	22	Hydrogenation of dehydroamino acid with H_2; less e.e. with 3-thienyl isomer	145
$C_{14}H_{13}NO_4$	 $(2\text{-furyl})CH_2\text{-}\underset{\displaystyle NHCOPh}{\underset{\vert}{C}}H\text{-}COOH$	[[Rh(cod)**Diop**]ClO_4	19	Hydrogenation of the corresponding dehydroamino acid with H_2	145
$C_{14}H_{14}N_2O_3$	 $(3\text{-quinolyl})CH_2\text{-}\underset{\displaystyle NHCOMe}{\underset{\vert}{C}}H\text{-}COOH$	[Rh(cod)**Diop**]ClO_4	70	Hydrogenation of the corresponding dehydroamino acid with H_2	145
$C_{14}H_{15}NO_4$	 $ArCH_2\text{-}\underset{\displaystyle Me}{\underset{\vert}{C}}H\text{-}COOEt$	$PdCl_2$/**303**; **Diop**, Rh catalysts	4, *R*	Hydrocarbethoxylation of (*E*)-*N*-propenylphthalimide; less e.e. with regioisomer	228
$C_{14}H_{16}$	 $2\text{-}C_{10}H_7\text{-}\underset{\displaystyle Me}{\underset{\vert}{C}}H\text{-}Et$	$NiCl_2$/**Prophos**	47.7, *R*	Cross-coupling of *s*-Bu Grignard with 2-naphthyl halide; less e.e. with 1-isomer	244
$C_{14}H_{17}NO_5$	 $ArCH_2\text{-}\underset{\displaystyle NHCOMe}{\underset{\vert}{C}}H\text{-}COOH$	$[Rh(nbd)_2]ClO_4$/**239**	85, *S*	Hydrogenation of dehydroamino acid ($Ar{=}3\text{-}MeO, 4\text{-}MeCOC_6H_3$) with H_2	109

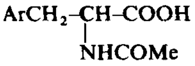
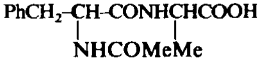
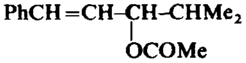
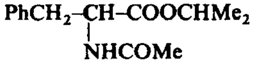
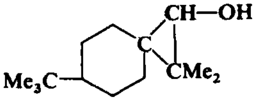
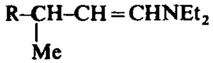
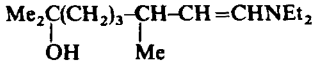
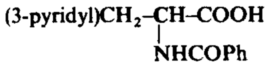
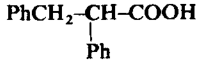
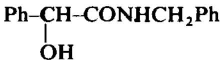
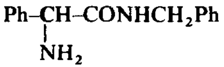
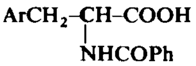
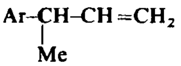
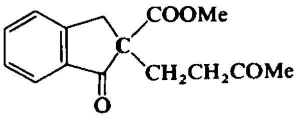
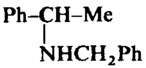
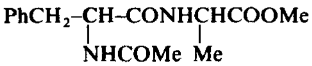
$C_{14}H_{17}NO_6$	 $\mathrm{ArCH_2{-}\underset{NHCOMe}{CH}{-}COOH}$	$[Rh(cod)Cl]_2$/**175**; **198**	88, *R*	Hydrogenation of dehydroamino acid (Ar = 3-MeO, 4-$MeCOOC_6H_3$) with H_2	132
$C_{14}H_{18}N_2O_4$	 $\mathrm{PhCH_2{-}\underset{NHCOMe}{CH}{-}CONH\underset{Me}{CH}COOH}$	$[Rh(cod)_2]BF_4$/**262**; **240**, **241**, **251**, **269**	96, *S*	Hydrogenation of Ac-ΔPhe-(S)-Ala-OH with H_2; double stereoselection	152 119
		$[Rh(cod)_2]BF_4$/**262**; **228**, **240**, **241**	96, *S*	As above; 92% e.e. R for substrate Ac-ΔPhe-(R)-Ala-OH	153
$C_{14}H_{18}O_2$	 $\mathrm{PhCH{=}CH{-}\underset{OCOMe}{CH}{-}CHMe_2}$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**285**	> 99, *R*	Allylic alkylation; kinetic resolution; recovered 1-styryl-2-methylpropyl acetate	260
$C_{14}H_{19}NO_3$	 $\mathrm{PhCH_2{-}\underset{NHCOMe}{CH}{-}COOCHMe_2}$	$[Rh(cod)_2]BF_4$/**240**; **241**	3, *S*	Hydrogenation of the corresponding dehydroamino acid with H_2	119
$C_{14}H_{26}O$		Cobalamin = **304**	[α] 0.5°	Reductive cyclization of unsaturated aldehyde; additionally regioisomer	234
$C_{14}H_{27}N$	 $\mathrm{R{-}\underset{Me}{CH}{-}CH{=}CHNEt_2}$	$[Rh(cod)$**Binap**$]ClO_4$; **Diop**, **BPPM**, **89**, **123**, **220**	99.3, *R*	Isomerization of diethylgeranylamine ($R = Me_2C{=}CHCH_2CH_2$); less e.e. for isomer	271 272
$C_{14}H_{29}NO$	 $\mathrm{Me_2\underset{OH}{C}(CH_2)_3{-}\underset{Me}{CH}{-}CH{=}CHNEt_2}$	$[Rh(cod)$**Binap**$]ClO_4$	[α] +12°	Isomerization of (*E*/*Z*)-*N*,*N*-diethyl-7-hydroxy-3,7-dimethyl-2-octenylamine	271
$C_{15}H_{14}N_2O_3$	 $\mathrm{(3\text{-}pyridyl)CH_2{-}\underset{NHCOPh}{CH}{-}COOH}$	$[Rh(cod)Cl]_2$/**Diop**	20	Hydrogenation of the corresponding dehydroamino acid with H_2	145
$C_{15}H_{14}O_2$	 $\mathrm{PhCH_2{-}\underset{Ph}{CH}{-}COOH}$	$[Rh(cod)$**185**$]BF_4/H_2NCHMePh$	55, *R*	Hydrogenation of α-phenylcinnamic acid with H_2; ligand Dioxop	116

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{15}H_{15}NO_2$	 $\mathrm{Ph{-}CH(OH){-}CONHCH_2Ph}$	$[Rh(cod)Cl]_2$/**220**; **182**	71, *S*	Hydrogenation of phenylglyoxyl-*N*-benylamide with H_2; peralkyl diphosphines	165
		$[Rh(C_8H_{14})_2Cl]_2$/**247**; **264**, **265**	47, *R*	As above; bis-dicyclohexylphosphine derivatives of Diop, Chiraphos	166
$C_{15}H_{16}N_2O$	 $\mathrm{Ph{-}CH(NH_2){-}CONHCH_2Ph}$	$[Rh(cod)Cl]_2$/**220**	[α] −29°	Hydrogenation of α-ketoxime-α-Ph-*N*-benzyl-acetamide with H_2	165
$C_{15}H_{16}N_2O_3$	 $\mathrm{ArCH_2{-}CH(NHCOPh){-}COOH}$	$[Rh(cod)Cl]_2$/**Diop**	33	Hydrogenation of dehydroamino acid [Ar = 2-(1-methyl)pyrrolyl) with H_2	145
$C_{15}H_{16}O$	 $\mathrm{Ar{-}CH(Me){-}CH{=}CH_2}$	$NiCl_2$/**Chiraphos**	89, *R*	Cross-coupling of 6-MeO-2-naphthyl Grignard with allylic ester	264
$C_{15}H_{16}O_4$		$Co(acac)_2$/**67**	66, *R*	Michael addition of Me 1-oxo-2-indanone carboxylate/vinyl methyl ketone	305
$C_{15}H_{17}N$	 $\mathrm{Ph{-}CH(NHCH_2Ph){-}Me}$	$[Rh(nbd)Cl]_2$/**231**; **Diop′**, **Dipamp**, **NMDPP**, **192**, **193**, **222**	72, *S*	Hydrogenation of *N*-benzyl aceto-phenone imine with H_2	187
		$[Rh(cod)Cl]_2$/**193**; **192**	73, *R*	As above; ligand BDPP = 2,4-bisdiphenylphosphinopentane	65
$C_{15}H_{20}N_2O_4$	 $\mathrm{PhCH_2{-}CH(NHCOMe){-}CONHCH(Me)COOMe}$	$[Rh(cod)_2]BF_4$/**240**; **269**	66, *R*	Hydrogenation of Ac-ΔPhe-(S)-Ala-OMe with H_2; double stereoselection	152

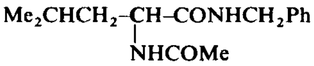
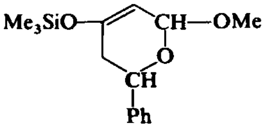
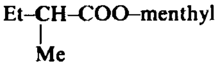
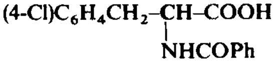
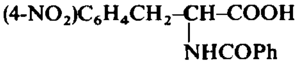
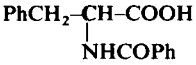
		[Rh(nbd) **281**]BF_4; **Diop**	94, *R*	As above; new Diop derived ligands	114
		[Rh(C_2H_4)$_2$Cl]$_2$/**Diop**′	83.8	As above; mathematical treatment of kinetic resolution	151
$C_{15}H_{22}N_2O_2$	 $Me_2CHCH_2\text{-}\underset{\displaystyle NHCOMe}{CH}\text{-}CONHCH_2Ph$	[Rh(nbd)Cl]$_2$/**Dipamp**; **Diop**′	95, *S*	Hydrogenation of dehydroamino acid *N*-benzylamide with H_2; preceding imidazole photooxidation/isomerization	100
$C_{15}H_{22}O_3Si$		Eu(**63**-H^+)$_3$	18, *R*	Cyclocondensation of benzaldehyde/trimethyl-siloxydiene; subsequent hydrolysis	310
$C_{15}H_{28}O_2$	 $Et\text{-}\underset{\displaystyle Me}{CH}\text{-}COO\text{-}menthyl$	$CoCl_2$/**Diop**/NEt_3	11.4, *R*	Hydrogenation of menthyl α-methylcrotonate with H_2	136
$C_{16}H_{14}ClNO_3$	 $(4\text{-}Cl)C_6H_4CH_2\text{-}\underset{\displaystyle NHCOPh}{CH}\text{-}COOH$	[Rh(cod)**Diop**]ClO_4; other Rh catalysts	26	Hydrogenation of 4-Cl benzamidocinnamic acid with H_2	129
$C_{16}H_{14}N_2O_5$	 $(4\text{-}NO_2)C_6H_4CH_2\text{-}\underset{\displaystyle NHCOPh}{CH}\text{-}COOH$	[Rh(cod)Cl]$_2$/**Diop**; other Rh catalysts	12	Hydrogenation of 4-NO_2 benzamidocinnamic acid with H_2	129
$C_{16}H_{15}NO_3$	 $PhCH_2\text{-}\underset{\displaystyle NHCOPh}{CH}\text{-}COOH$	[Rh(**Binap**)]ClO_4	100, *S*	Hydrogenation of (*Z*)-α-*N*-benzamidocinnamic acid with H_2; less e.e. with (*E*)-isomer	45
		[Rh(cod)Cl]$_2$/**175**; **198**	86, *R*	As above; catalysis in an aqueous–organic two-phase system	132
		[Rh(cod)Cl]$_2$/**186**	100	As above; new bisphosphine ligand Dpcp	64
		Ru_2Cl_4(**Binap**)$_2NEt_3$	92, *S*	As above; less e.e. with (*E*)-isomer	106
		[Rh(cod)Cl]$_2$/**143**/NEt_3	80, *R*	As above; new L-rhamnose derived ligand	107

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		$[Rh(nbd)_2]ClO_4$/Cu(**239**)Cl; **239**	94, *S*	As above; new L-threonine derived NPP ligand; X-ray structure of Cu complex	109
		$[Rh(nbd)Cl]_2$/[Cu(**278**)Cl]$_n$; **192**	93, *R*	As above; new bis-diphenylphosphinite ligand; efficient in enamide hydrogenation	110
		[Rh(nbd)**Diop**]BF_4; **237**, **238**	62, *R*	As above; new Diop derived ligands	114
		[Rh(nbd)**193**]ClO_4; **192**, other Rh catalysts	88	As above; new ligand BDPP = 2,4-bisdiphenylphosphinopentane	65
		$[Rh(nbd)Cl]_2$/**201**	38, *S*	As above; new D-mannitol derived ligand	115
		[Rh(cod)**185**]BF_4	33, *S*	As above; ligand Dioxop; mechanism	116
		$[Rh(C_8H_{14})_2Cl]_2$/**294**; **299**	95, *R*	As above; new bisdiphenylphosphine derivative of 2,2′-diamino-1,1′-binaphthyl	117
		[Rh(nbd)**125**]PF_6/NEt_3; **127**	77, *S*	As above; new PP and AsAs ligands with chiral P and As atoms	118
		$[Rh(cod)_2]BF_4$/**240**, **228**, **241**	40, *S*	As above; electrostatic interaction substrate/ligand; model	119
		$[Rh(cod)Cl]_2$/**Norphos**; **Prophos**, **Diop**, **BPPFA**	88.9, *S*	As above; attempted e.e. calculation with Ruch–Ugi model	121
		[Rh(cod)**Diop**]ClO_4; other Rh catalysts	64	As above; isolated cationic catalyst better than *in situ* neutral catalyst	129

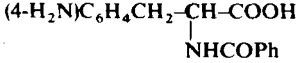
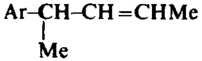
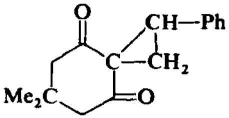
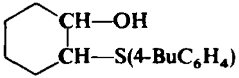
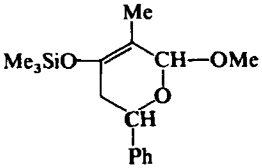
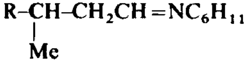
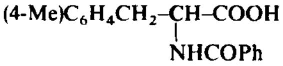
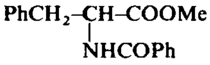
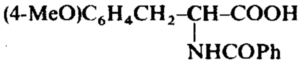
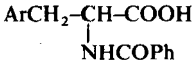
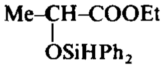
		$[Rh(hexadiene\text{-}1.5)Cl]_2$/**87**; **65**, **72**, **84**, **85**, **98**, **106**, **111**, **140**, **141**, **151**, **162**, **163**,	68, *R*	As above; new PN and AsN ligands; change of product configuration with ligand concentration	104
		[Rh(nbd)**Prophos**]ClO_4; **Diop**′	80, L	As above; ^{11}C-labeled at C-3; Na-derivative	108
$C_{16}H_{16}N_2O_3$	 $(4\text{-}H_2N)C_6H_4CH_2\text{-}\underset{NHCOPh}{CH}\text{-}COOH$	[Rh(cod)**Diop**]ClO_4; other Rh catalysts	57	Hydrogenation of 4-NH_2 benzamidocinnamic acid with H_2	129
$C_{16}H_{18}O$	 $Ar\text{-}\underset{Me}{CH}\text{-}CH{=}CHMe$	$NiCl_2$/**Chiraphos**	68, *R*	Cross-coupling of 2-(6-MeO)naphthyl Grignard/allylic ester	264
$C_{16}H_{18}O_2$		Cu(**55**-H^+)$_2$; **46**, **51**′, **314**	100	Cyclopropanation of styrene/2-diazodimedone; **314** = polymer bound ligand	78
$C_{16}H_{24}OS$		Zn(TA–2H^+), heterogeneous system	52, *R*,*R*	Ring-opening of cyclohexene oxide with 4-*t*-BuC_6H_4SH	72
$C_{16}H_{24}O_3Si$		Eu(**63**-H^+)$_3$	15, *R*	Cyclocondensation of benzaldehyde/trimethylsiloxydiene; subsequent hydrolysis	310
$C_{16}H_{29}N$	 $R\text{-}\underset{Me}{CH}\text{-}CH_2CH{=}NC_6H_{11}$	[Rh(cod)**Binap**′]ClO_4; **Diop**, **89**, **123**, **220**	96, *R*	Isomerization of cyclohexylgeranylamine ($R = Me_2C{=}CHCH_2CH_2$)	271
$C_{17}H_{17}NO_3$	 $(4\text{-}Me)C_6H_4CH_2\text{-}\underset{NHCOPh}{CH}\text{-}COOH$	[Rh(cod)**Diop**]ClO_4; other Rh catalysts	85	Hydrogenation of 4-Me benzamidocinnamic acid with H_2	129

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
	 $\mathrm{PhCH_2{-}\underset{NHCOPh}{CH}{-}COOMe}$	[Rh(**Binap**)]ClO_4	93, *R*	Hydrogenation of methyl (*Z*)-α-benzamidocinnamate with H_2	45
		[Rh(cod)Cl]$_2$/**186**	100	As above; new bisphosphine ligand Dpcp	64
		[Rh(nbd)**193**]ClO_4; **192**, other Rh catalysts	79	As above; new ligand BDPP = 2,4-bisdiphenylphosphinopentane	65
		[Rh(C_8H_{14})$_2$Cl]$_2$/**294**	89, *R*	As above; new bisdiphenylphosphine derivative of 2,2′-diamino-1,1′-binaphthyl	117
		[Rh(cod)$_2$]BF_4/**240**; **241**	28, *S*	As above; electrostatic interaction substrate/ligand; model	119
		[Rh(cod)Cl]$_2$/**Norphos**; **Prophos**, **Diop′**, **BPPFA**	84.6, *S*	As above; attempted e.e. calculation with Ruch–Ugi model	121
		$Rh_6(CO)_{10}$(**Diop**)$_3$	3, *R*	As above; cluster catalysis/fragment catalysis	131
$C_{17}H_{17}NO_4$	 $\mathrm{(4\text{-}MeO)C_6H_4CH_2{-}\underset{NHCOPh}{CH}{-}COOH}$	[Rh(cod)**Diop**]ClO_4; other Rh catalysts	57	Hydrogenation of 4-MeO-benzamidocinnamic acid with H_2	129
$C_{17}H_{17}NO_5$	 $\mathrm{ArCH_2{-}\underset{NHCOPh}{CH}{-}COOH}$	[Rh(**Binap**)]ClO_4	79, *R*	Hydrogenation of (*Z*)-dehydroamino acid (Ar = 4-OH, 3-MeOC_6H_3) with H_2	45
$C_{17}H_{20}O_3Si$	 $\mathrm{Me{-}\underset{OSiHPh_2}{CH}{-}COOEt}$	[Ir(nbd)Cl]$_2$/**159**	7	Hydrosilylation of Et pyrurate/Ph_2SiH_2; hydrolysis→α-hydroxy ester	206
$C_{17}H_{22}N_2O_6$	Ac-L-Tyr(Ac)-D-Ala-OMe	[Rh(nbd)$_2$]ClO_4/**Dipamp**; **259**	96.8, L	Hydrogenation of Ac-ΔTyr(Ac)-D-Ala-OMe with H_2	154

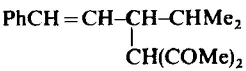
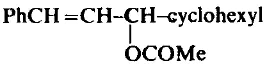
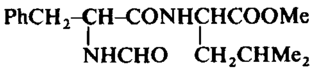
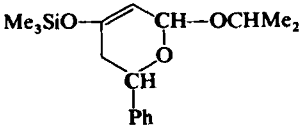
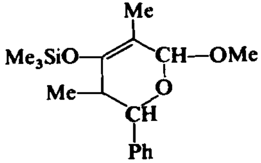
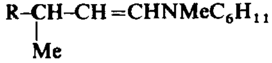
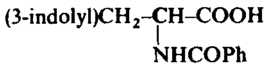
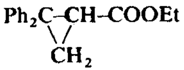
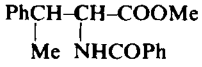
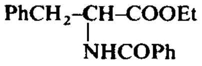
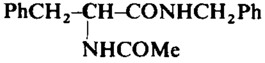
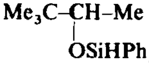
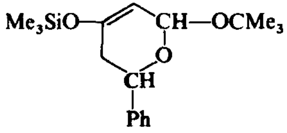
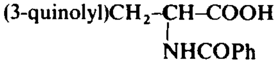
$C_{17}H_{22}O_2$	 $\mathrm{PhCH{=}CH{-}\underset{\displaystyle CH(COMe)_2}{CH}{-}CHMe_2}$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**285**	> 98, *S*	Allylic alkylation of J-styryl 2-Me-propylacetate with $NaCH(COMe)_2$; kinetic resolution; $k_S/k_R = 14$	260
	 $\mathrm{PhCH{=}CH{-}\underset{\displaystyle OCOMe}{CH}{-}cyclohexyl}$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**285**	61, *R*	Kinetic resolution in the allylic alkylation of styryl cyclohexylmethylacetate with $NaCH(COMe)_2$; $k_S/k_R = 7$	260
$C_{17}H_{24}N_2O_4$	 $\mathrm{PhCH_2{-}\underset{\displaystyle NHCHO}{CH}{-}CONH\underset{\displaystyle CH_2CHMe_2}{CH}COOMe}$	$[Rh(nbd)_2]ClO_4$/**Dipamp**; **259**	96.8, *S*	Hydrogenation of *N*-formyl-ΔPhe-(*S*)-Leu-OMe with H_2	154
$C_{17}H_{26}O_3Si$		Eu(**63**-H^+)$_3$	28, *R*	Cyclocondensation of benzaldehyde/trimethylsiloxydiene; subsequent hydrolysis	310
		Eu(**63**-H^+)$_3$	36, *R*	Cyclocondensation of benzaldehyde/trimethylsiloxydiene; subsequent hydrolysis	310
$C_{17}H_{31}N$	 $\mathrm{R{-}\underset{\displaystyle Me}{CH}{-}CH{=}CHNMeC_6H_{11}}$	[Rh(**Binap**')sol_2]ClO_4	91, *S*	Isomerization of cyclohexylmethylgeranylamine ($R = Me_2C{=}CHCH_2CH_2$)	271
$C_{18}H_{16}N_2O_3$	 $\mathrm{(3\text{-}indolyl)CH_2{-}\underset{\displaystyle NHCOPh}{CH}{-}COOH}$	$[Rh(cod)Cl]_2$/**Diop**	32	Hydrogenation of the corresponding dehydroamino acid with H_2	145
$C_{18}H_{18}O_2$	 $\mathrm{Ph_2C{-}CH{-}COOEt}$ (bridged by CH_2)	$Cu(OAc)_2$/**176**; **34**, **42**, **44**, **58**, **76**, **77**, **78**, **82**, **83**, **90–95**, **115**, **133**, **134**, **136**, **137**, **150**, **183**, **184**, **242**	65.6, *S*	Cyclopropanation of 1,1-diphenylethylene and ethyl diazo acetate, 7 further ligands with e.e. < 1%	229

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		$Cu(OAc)_2$/**77**	3, *S*	As above; tropolone derived ligand	208
$C_{18}H_{19}NO_3$	 $PhCH(Me)-CH(NHCOPh)-COOMe$	[Ir(cod)PhCN(**NMDPP**)]ClO_4	18.9	Hydrogenation of tetra-substituted (*Z*)-enamide with H_2; less e.e. for (*E*)-isomer	147
	 $PhCH_2-CH(NHCOPh)-COOEt$	[Rh(nbd)**125**]PF_6/NEt_3; **127**	36, *S*	Hydrogenation of ethyl (*Z*)-α-*N*-benzamidocinnamate with H_2; P and As ligands	118
$C_{18}H_{20}N_2O_2$	 $PhCH_2-CH(NHCOMe)-CONHCH_2Ph$	$[Rh(nbd)Cl]_2$/**Dipamp**	96, *S*	Hydrogenation of (*Z*)-α-*N*-acetamidocinnamic acid *N*-benzylamide with H_2	100
$C_{18}H_{24}OSi$	 $Me_3C-CH(OSiHPh_2)-Me$	$[Rh(cod)Cl]_2$/**149**; **Diop**′, **33**, **54**, **62**, **66**, **71**, **80**, **81**, **86**, **100**, **107**, **109**, **116**, **117**, **126**	61.1, *S*	Hydrosilylation of *t*-butyl methyl ketone/H_2SiPh_2, hydrolysis→3,3-dimethylbutan-2-ol; pyridine imine and amine ligands	210
		$[Rh(cod)Cl]_2$/**39**; **31**	69, *R*	As above; new pyridine thiazolidine ligands	60
$C_{18}H_{28}O_3Si$		Eu(**63**-H^+)$_3$	38, *R*	Cyclocondensation of benzaldehyde/trimethylsiloxydiene; subsequent hydrolysis	310
$C_{19}H_{16}N_2O_3$	 (3-quinolyl)$CH_2-CH(NHCOPh)-COOH$	$[Rh(cod)Cl]_2$/**Diop**	55	Hydrogenation of the corresponding dehydroamino acid with H_2	145

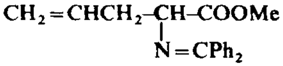
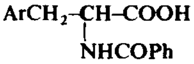
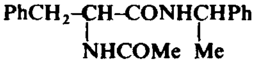
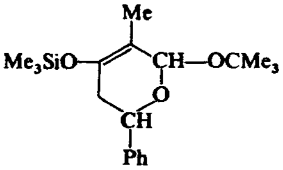
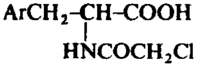
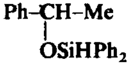
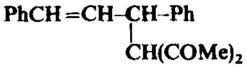
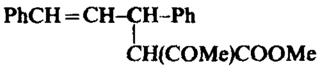
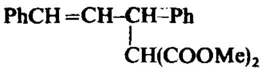
$C_{19}H_{19}NO_2$	 $\mathrm{CH_2{=}CHCH_2{-}\underset{\displaystyle N{=}CPh_2}{CH}{-}COOMe}$	Pd(dba)$_2$/**Diop**; **Norphos**, **Binap**, **Prophos**, **BPPM**, **Chiraphos**, **Dipamp**, **64**, **96**, **102**, **225**	57, *R*	Alkylation of allyl acetate with Li derivative of glycine methyl ester benzophenone imine; $H_2O \rightarrow$ amino acid ester	261
$C_{19}H_{19}NO_6$	 $\mathrm{ArCH_2{-}\underset{\displaystyle NHCOPh}{CH}{-}COOH}$	[Rh(**Binap**)]ClO$_4$	70, *R*	Hydrogenation of dehydroamino acid (Ar = 3-MeO, 4-MeCOOC$_6$H$_3$) with H$_2$	45
$C_{19}H_{22}N_2O_2$	 $\mathrm{PhCH_2{-}\underset{\displaystyle NHCOMe}{CH}{-}CONH\underset{\displaystyle Me}{CH}Ph}$	PdCl$_2$/**19**/H$_2$; *in situ* catalysts	50, *S*	Reductive aminolysis of 2-Me-4-PhCH-oxazol-5-one with (*S*)-H$_2$NCHMePh	308 309
$C_{19}H_{25}N_3O_7$	Ac-(D)-Tyr(Ac)-(D)-Ala-Gly-OMe	[Rh(nbd)$_2$]ClO$_4$/**259**	99.4, D	Hydrogenation of Ac-Δ-Tyr(Ac)-(D)-Ala-Gly-OMe with H$_2$	154
$C_{19}H_{30}O_3Si$		Eu(**63**-H$^+$)$_3$	58, *R*	Cyclocondensation of benzaldehyde/trimethylsiloxydiene; subsequent hydrolysis	310
$C_{20}H_{20}ClNO_6$	 $\mathrm{ArCH_2{-}\underset{\displaystyle HNCOCH_2Cl}{CH}{-}COOH}$	[Rh(cod)Cl]$_2$/**Diop**′	80, *S*	Hydrogenation of dehydroamino acid (Ar = 2-MeO, 5-PhCH$_2$OOCC$_6$H$_3$) with H$_2$	149
$C_{20}H_{20}OSi$	 $\mathrm{Ph{-}\underset{\displaystyle OSiHPh_2}{CH}{-}Me}$	Cu(PhCOO)/**Norphos**′; **Diop**, **BPPFA**, Cu catalysts	38.8, *R*	Hydrosilylation of acetophenone with H$_2$SiPh$_2$, hydrolysis → 1-phenylethanol	209
		[Rh(cod)Cl]$_2$/**31**; **107**	86.7, *R*	As above; new pyridine imine and amine ligands; 37 ligands and 18 isolated Rh and Pt complexes tested	210 59
		[Rh(cod)Cl]$_2$/**40**; **18**, **23**, **26**, **29–31**, **39**, **41**, **47**, **48**, **50**, **52**, **57**, **59**, **60**, **147**	97.6, *R*	As above; new pyridine thiazolidine ligands; ligands epimerized at C-2 in the thiazolidine ring are as efficient as pure diastereomers	60 59

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
		$[Rh(cod)Cl]_2$/**172**; **170**, **298**, other Rh catalysts	52.7, *S*	As above; new PN ligands, e.e. increases with decreasing catalyst concentration	122
		$[Rh(cod)Cl]_2$/**157**	19.6, *R*	As above; new pyrrole amine derived PN ligand	207
		$[Rh(cod)Cl]_2$/**58**; **118**	0.3, *R*	As above; racemization of ligand **118** during catalysis	123
		$[Rh(cod)Cl]_2$/**275′**	9.3, *S*	As above; one of the P atoms of Diop blocked by $CpMn(CO)_2$ fragment	124
		Rh(cod)(**77**-H$^+$)/**Diop**; **Norphos′**, **148**, other Rh catalysts	32.8, *R*	As above; e.e. with **77**, **148** below 1%, no double stereoselection	208
$C_{20}H_{20}O_2$	 $\mathrm{PhCH{=}CH{-}\underset{CH(COMe)_2}{\underset{\vert}{C}}H{-}Ph}$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**285**; **Diop**, **BPPM**, **BPPFA**, **255**, **266**, **282**, **284**	90, *S*	Allylic alkylation of (*E*)-1,3-diphenyl-3-acetoxy-1-propene with $NaCH(COMe)_2$	259
$C_{20}H_{20}O_3$	 $\mathrm{PhCH{=}CH{-}\underset{CH(COMe)COOMe}{\underset{\vert}{C}}H{-}Ph}$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**285**	83, *S*	Allylic alkylation of (*E*)-1,3-diphenyl-3-acetoxy-1-propene with NaCH(COMe)COOMe	259
$C_{20}H_{20}O_4$	 $\mathrm{PhCH{=}CH{-}\underset{CH(COOMe)_2}{\underset{\vert}{C}}H{-}Ph}$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**285**	48, *S*	Allylic alkylation of (*E*)-1,3-diphenyl-3-acetoxy-1-propene with $NaCH(COOMe)_2$	259
		Pd-acetate/**292**	55	Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with $NaCH(COOMe)_2$	258
		$[(\eta^3\text{-}C_3H_5)Pd($**Chiraphos**$)]ClO_4$	22	As above; extensive mechanistic study	250

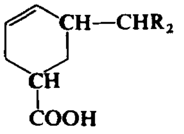
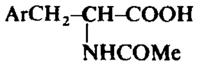
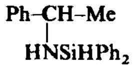
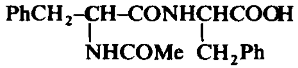
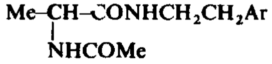
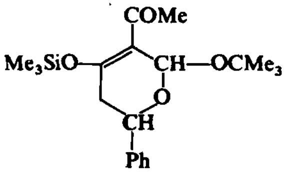
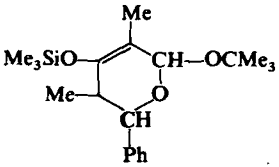
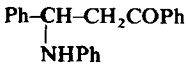
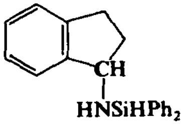
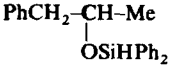
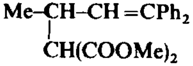
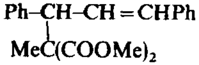
$C_{20}H_{20}O_6S_2$		Pd-acetate/**307**, **Diop**, **Binap**, **Chiraphos**, **292**	69	Allylic alkylation of cyclohexen-4-yl-1,3-lactone with $NaCH(SO_2Ph)_2$ ($R = SO_2Ph$)	258
$C_{20}H_{21}NO_6$	 $\mathrm{ArCH_2{-}\underset{\displaystyle NHCOMe}{\underset{\vert}{CH}}{-}COOH}$	[Rh(cod)**Dipamp**]BF_4	> 98	Hydrogenation of dehydroamino acid with H_2 ($Ar = 2\text{-}MeO, 5\text{-}PhCH_2OOCC_6H_3$)	149
$C_{20}H_{21}NSi$	 $\mathrm{Ph{-}\underset{\displaystyle HNSiHPh_2}{\underset{\vert}{CH}}{-}Me}$	$[Rh(cod)Cl]_2$/**Diop**; **190**	19.4, *R*	Hydrosilylation of acetophenone oxime/ H_2SiPh_2; hydrolysis → primary amine	212 211
$C_{20}H_{22}N_2O_4$	 $\mathrm{PhCH_2{-}\underset{\displaystyle NHCOMe}{\underset{\vert}{CH}}{-}CONH\underset{\displaystyle CH_2Ph}{\underset{\vert}{C}}HCOOH}$	$[Rh(cod)_2]BF_4$/**261**; **228**, **240**, **241**, **262**, **269**	> 98, *S*	Hydrogenation of Ac-ΔPhe-(S)-Phe-OH with H_2; double stereoselection	152 119
		[Rh(nbd)**281**]BF_4; **Diop**, **237**, **238**, **279**, **297**	72, *R*	As above; new Diop derived ligands	114
		$[Rh(cod)_2]BF_4$/**262**; **228**, **240**, **241**, **269**	> 98, *S*	As above; 86% e.e. (*R*) for substrate Ac-ΔPhe-(R)-Phe-OH	153
$C_{20}H_{24}N_2O_3$	 $\mathrm{Me{-}\underset{\displaystyle NHCOMe}{\underset{\vert}{CH}}{-}CONHCH_2CH_2Ar}$ $Ar = (4\text{-}PhCH_2O)C_6H_4$	$[Rh(nbd)Cl]_2$/**Dipamp**; **Diop′**	88, *S*	Hydrogenation of dehydroamino acid amide with H_2; preceding imidazole photo-oxidation/isomerization	100
$C_{20}H_{26}F_3N_3O_5$	TFA-Gly-(S)-Phe-(*S*)-Leu-OMe	$[Rh(nbd)_2]ClO_4$/**259**	23, *R*	Hydrogenation of TFA-Gly-ΔPhe-(*S*)-Leu-OMe with H_2	154
$C_{20}H_{30}O_4Si$		Eu(**63**-H^+)$_3$	33, *R*	Cyclocondensation of benzaldehyde/trimethylsiloxydiene; subsequent hydrolysis	310

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{20}H_{32}O_3Si$		Eu(**63**-H$^+$)$_3$	55, *R*	Cyclocondensation of benzaldehyde/trimethylsiloxydiene; subsequent hydrolysis	310
$C_{21}H_{19}NO$	 $Ph-\underset{NHPh}{CH}-CH_2COPh$	Cu(**79**-H$^+$)$_2$; **20**, **73**, **88**, **104**, **130**	[α] −5°	Michael addition of aniline and chalcone; product recrystallized	306
$C_{21}H_{21}NSi$		[Rh(cod)Cl]$_2$/**Diop**	12.9, *R*	Hydrosilylation of indanone oxime/H_2SiPh_2; hydrolysis → primary amine	212
$C_{21}H_{22}OSi$	 $PhCH_2-\underset{OSiHPh_2}{CH}-Me$	[Rh(cod)Cl]$_2$/**116**; **Diop′**, **33**, **54**, **66**, **71**, **80**, **81**, **86**, **100**, **107**, **109**, **116**, **117**, **124**, **126**	56.6, *S*	Hydrosilylation of benzyl methyl ketone with H_2SiPh_2, hydrolysis → 1-Ph-propan-2-ol; pyridine imine and amine ligands	210
		[Rh(cod)Cl]$_2$/**107**; **39**	53, *R*	As above; pyridine thiazolidine ligands	60
$C_{21}H_{22}O_4$	 $Me-\underset{CH(COOMe)_2}{CH}-CH=CPh_2$	[(η^3-C_3H_5)Pd(**Norphos**)]ClO_4; **Chiraphos**, **Prophos**, **Dipamp**, **230**	76	Allylic alkylation of 4,4-diphenyl-3-buten-2-yl acetate with $NaCH(COOMe)_2$	250
	 $Ph-\underset{MeC(COOMe)_2}{CH}-CH=CHPh$	Pd-acetate/**292**; **Binap**	68	Allylic alkylation of 1,3-diphenylallyl acetate with $NaCMe(COOMe)_2$	258

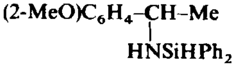
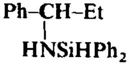
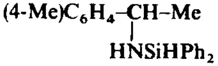
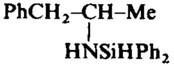
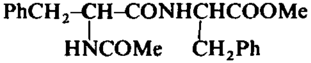
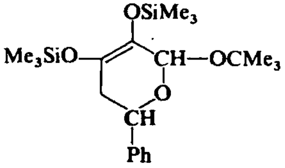
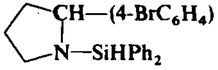
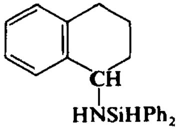
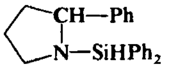
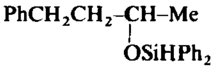
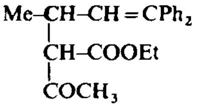
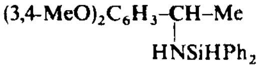
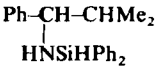
$C_{21}H_{23}NOSi$	 $(2\text{-MeO})C_6H_4\text{–}\underset{\text{HNSiHPh}_2}{\underset{\mid}{\text{CH}}}\text{–Me}$	$[Rh(cod)Cl]_2$/**Diop**; **Norphos**	16.5, *R*	Hydrosilylation of 2-MeO-acetophenone oxime/H_2SiPh_2; less e.e. with 4-MeO isomer	212
$C_{21}H_{23}NSi$	 $\text{Ph–}\underset{\text{HNSiHPh}_2}{\underset{\mid}{\text{CH}}}\text{–Et}$	$[Rh(cod)Cl]_2$/**Diop**	7.6, *R*	Hydrosilylation of propiophenone oxime/H_2SiPh_2; hydrolysis → primary amine	211
	 $(4\text{-Me})C_6H_4\text{–}\underset{\text{HNSiHPh}_2}{\underset{\mid}{\text{CH}}}\text{–Me}$	$[Rh(cod)Cl]_2$/**Diop**	8.2, *R*	Hydrosilylation of 4-Me-acetophenone oxime/H_2SiPh_2; hydrolysis → amine	212
	 $PhCH_2\text{–}\underset{\text{HNSiHPh}_2}{\underset{\mid}{\text{CH}}}\text{–Me}$	$[Rh(cod)Cl]_2$/**Diop**	7.1, *S*	Hydrosilylation of benzyl methyl ketoxime/H_2SiPh_2; hydrolysis → amine	212
$C_{21}H_{24}N_2O_4$	 $PhCH_2\text{–}\underset{\text{HNCOMe}}{\underset{\mid}{\text{CH}}}\text{–CONH}\underset{\text{CH}_2\text{Ph}}{\underset{\mid}{\text{CH}}}\text{COOMe}$	$[Rh(cod)_2]BF_4$/**269**; **240**	30, *R*	Hydrogenation of Ac-ΔPhe-(R)-Phe-OMe with H_2; less e.e. for (*S*)-Phe isomer	152 119
		$[Rh(cod)_2]BF_4$/**269**; **240**	10, *S*	Hydrogenation of Ac-ΔPhe-(S)-Phe-OMe with H_2; double stereoselection	153
		[Rh(nbd)**281**]BF_4; **Diop**	94, *R*	As above; new Diop derived ligand	114
$C_{21}H_{36}O_4Si$		Eu(**63**-H^+)$_3$	42, *R*	Cyclocondensation of benzyldehyde/trimethylsiloxydiene; subsequent hydrolysis	310
$C_{22}H_{22}BrNSi$		$[Rh(cod)Cl]_2$/**Diop**	60, *R*	Hydrosilylation of 4-Br-phenyl-3,4-dihydro-2*H*-pyrrole with H_2SiPh_2	213

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{22}H_{23}NSi$		$[Rh(cod)Cl]_2$/**Diop**	18.7, *R*	Hydrosilylation of 1-tetralone oxime/H_2SiPh_2; hydrolysis → primary amine	212
		$[Rh(cod)Cl]_2$/**Diop**	64, *R*	Hydrosilylation of phenyl-3,4-dihydro-2*H*-pyrrole with H_2SiPh_2	213
$C_{22}H_{24}OSi$	 $PhCH_2CH_2\text{-}CH(OSiHPh_2)\text{-}Me$	$[Rh(cod)Cl]_2$/**39**; **40**	55	Hydrosilylation of 4-phenylbutan-2-one/H_2SiPh_2; hydrolysis → 4-phenylbutan-2-ol	60
$C_{22}H_{24}O_3$	 $Me\text{-}CH(CH(COOEt)COCH_3)\text{-}CH{=}CPh_2$	$[(\eta^3\text{-}C_3H_5)Pd($**Chiraphos**$)]ClO_4$	67	Allylic alkylation of 4,4-diphenyl-3-buten-2-yl acetate with $NaCH(COOEt)COCH_3$; mechanism	250
$C_{22}H_{25}NO_2Si$	 $(3,4\text{-}MeO)_2C_6H_3\text{-}CH(HNSiHPh_2)\text{-}Me$	$[Rh(cod)Cl]_2$/**Diop**	6.5, *R*	Hydrosilylation of $(3,4\text{-}MeO)_2$-phenyl methyl ketoxime/H_2SiPh_2	212
$C_{22}H_{25}NSi$	 $Ph\text{-}CH(HNSiHPh_2)\text{-}CHMe_2$	$[Rh(cod)Cl]_2$/**Diop**	18.9, *R*	Hydrosilylation of isobutyrophenone oxime/H_2SiPh_2; hydrolysis → amine	211 212
$C_{22}H_{33}N_4O_5$	BOC-Gly-(S)-Phe-(*S*)-Leu-NH_2	$[Rh(nbd)_2]ClO_4$/**BPPM'**; **Dipamp**	85.2, *S*	Hydrogenation of BOC-Gly-ΔPhe-(*S*)-Leu-NH_2 with H_2	154

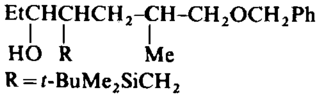
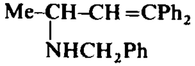
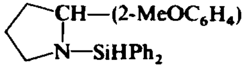
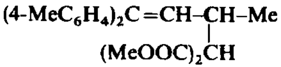
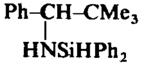
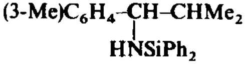
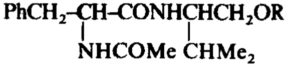
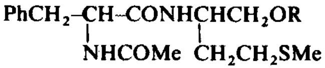
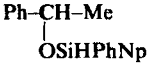
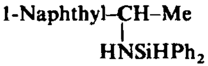
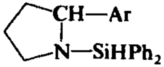
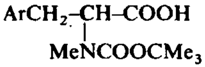
$C_{22}H_{40}O_2Si$	 $Et\underset{HO}{CH}\underset{R}{CH}CH_2\text{-}\underset{Me}{CH}\text{-}CH_2OCH_2Ph$ $R = t\text{-}BuMe_2SiCH_2$	[Rh(**Binap'**)]$^+$	94, *S*	Hydrogenation of the corresponding homoallylic alcohol with H_2; OH-directed 1,3-stereocontrol	159
$C_{23}H_{23}N$	 $Me\text{-}\underset{NHCH_2Ph}{CH}\text{-}CH{=}CPh_2$	[(η^3-C_3H_5)Pd(**Chiraphos**)]ClO_4	63	Allylation of benzylamine with 4,4-diphenyl-3-buten-2-yl acetate	250
$C_{23}H_{25}NOSi$		[Rh(cod)Cl]$_2$/**Diop**	31, *R*	Hydrosilylation of 2-MeO-phenyl-3,4-dihydro-2*H*-pyrrole with H_2SiPh_2	213
$C_{23}H_{26}O_4$	 $(4\text{-}MeC_6H_4)_2C{=}CH\text{-}\underset{(MeOOC)_2CH}{CH}\text{-}Me$	[(η^3-C_3H_5)Pd(**Chiraphos**)]ClO_4	64, *S*	Allylic alkylation of 4,4-bis(*p*-tolyl)-3-buten-2-yl acetate with $NaCH(COOMe)_2$	251
$C_{23}H_{27}NSi$	 $Ph\text{-}\underset{HNSiHPh_2}{CH}\text{-}CMe_3$	[Rh(cod)Cl]$_2$/**Diop**; **Norphos**	36, *S*	Hydrosilylation of phenyl *t*-butyl ketoxime/H_2SiPh_2; hydrolysis → amine	212
		[Rh(cod)Cl]$_2$/**Diop**; **BPPFA**, **Norphos**, **Prophos**, **39**, **62**	23.1, *S*	Hydrosilylation of phenyl *t*-butyl ketimine/H_2SiPh_2; hydrolysis → amine	212
	 $(3\text{-}Me)C_6H_4\text{-}\underset{HNSiPh_2}{CH}\text{-}CHMe_2$	[Rh(cod)Cl]$_2$/**Diop**; **BPPFA**, **Norphos**, **Prophos**, **39**, **62**	13.8, *R*	Hydrosilylation of 3-Me-phenyl *i*-propyl ketimine/H_2SiPh_2; less e.e. for 2-Me isomer	212
$C_{23}H_{30}N_2O_3$	 $PhCH_2\text{-}\underset{NHCOMe}{CH}\text{-}CONH\underset{CHMe_2}{CH}CH_2OR$	[Rh(nbd)$_2$]ClO_4/**BPPM'**; **Diop**, **259**	97.2, *S*	Hydrogenation of Ac-ΔPhe-β-valinol benzyl ether with H_2 ($R = CH_2Ph$)	154
$C_{23}H_{30}N_2O_3S$	 $PhCH_2\text{-}\underset{NHCOMe}{CH}\text{-}CONH\underset{CH_2CH_2SMe}{CH}CH_2OR$	[Rh(nbd)$_2$]ClO_4/**BPPM'**; **Diop**, **259**	91, *S*	Hydrogenation of Ac-ΔPhe-β-methioninol benzyl ether with H_2 ($R = CH_2Ph$)	154

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{23}H_{35}N_3O_6$	BOC-Gly-(S)-Phe-(*S*)-Leu-OMe	[Rh(nbd)$_2$]ClO$_4$/**Dipamp**; **BPPM**, **245**, **259**	97.8, *S*	Hydrogenation of BOC-Gly-ΔPhe-(*S*)-Leu-OMe with H_2; dideuteration	154
$C_{23}H_{36}N_4O_5$	BOC-(*S*)-Ala-(S)-Phe-(*S*)-Leu-NH$_2$	[Rh(nbd)$_2$]ClO$_4$/**Dipamp**; **BPPM**	95, *S*	Hydrogenation of BOC-(*S*)-Ala-ΔPhe-(*S*)-Leu-NH$_2$ with H_2	154
$C_{24}H_{22}OSi$	 $\mathrm{Ph{-}\underset{OSiHPhNp}{CH}{-}Me}$	Cu(PhCOO)/**Norphos**′; **Diop**	16.3, *S*	Hydrosilylation of acetophenone/H_2Si-PhNp; hydrolysis→1-phenylethanol	209
		[Rh(cod)Cl]$_2$/**107**; **Norphos**′, **62**, **80**, **124**	67, *S*	As above; new pyridine imine ligands	210
		[Rh(cod)Cl]$_2$/**39**	46, *R*	As above; new pyridine thiazolidine ligand	60
$C_{24}H_{23}NSi$	 $\mathrm{1\text{-}Naphthyl{-}\underset{HNSiHPh_2}{CH}{-}Me}$	[Rh(cod)Cl]$_2$/**Diop**	16.2, *R*	Hydrosilylation of 1-naphthyl methyl ketoxime/H_2SiPh_2; less e.e. for 2-isomer	212
$C_{24}H_{27}NO_2Si$		[Rh(cod)Cl]$_2$/**Diop**	33, *R*	Hydrosilylation of (3,4-MeO)$_2$-phenyl-3,4-dihydro-2*H*-pyrrole with H_2SiPh_2	213
$C_{24}H_{30}N_2O_6$	CBZ-L-Phe-L-Leu-OMe	[Rh(nbd)$_2$]ClO$_4$/**Dipamp**	95.6, L	Hydrogenation of CBZ-ΔPhe-L-Leu-OMe with H_2; double stereoselection	154
$C_{24}H_{29}NO_7$	 $\mathrm{ArCH_2{-}\underset{MeNCOOCMe_3}{CH}{-}COOH}$	[Rh(cod)Cl]$_2$/**Diop**′	> 98, *S*	Hydrogenation of dehydroamino acid (Ar = 2-MeO, 5-PhCH$_2$OOCC$_6$H$_3$) with H_2	149

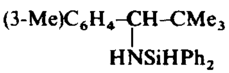
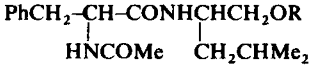
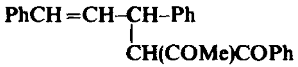
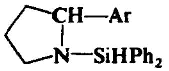
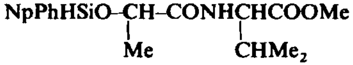
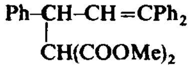
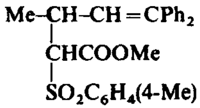
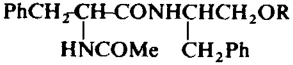
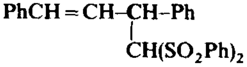
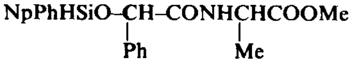
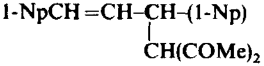
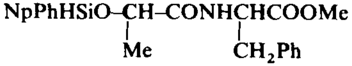
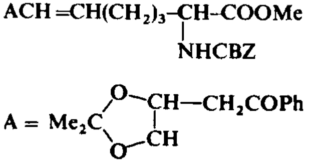
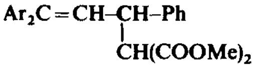
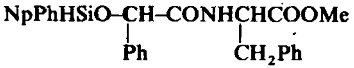
$C_{24}H_{29}NSi$	 $(3\text{-Me})C_6H_4\text{-}\underset{\substack{\mid\\ HNSiHPh_2}}{CH}\text{-}CMe_3$	[Rh(cod)Cl]$_2$/**Diop**	13.2, *S*	Hydrosilylation of 3-Me-phenyl *t*-butyl ketimine/H_2SiPh_2; less e.e. for 2-isomer	212
$C_{24}H_{32}N_2O_3$	 $PhCH_2\text{-}\underset{\substack{\mid\\ HNCOMe}}{CH}\text{-}CONH\underset{\substack{\mid\\ CH_2CHMe_2}}{CH}CH_2OR$	[Rh(nbd)$_2$]ClO$_4$/**BPPM'**; **Diop'**, **259**	98.2, *S*	Hydrogenation of Ac-ΔPhe-*β*-leucinol benzyl ether with H_2 ($R = CH_2Ph$)	154
$C_{24}H_{37}N_3O_6$	BoC-(*S*)-Ala-(**R**)-Phe-(*S*)-Leu-OMe	[Rh(nbd)$_2$]ClO$_4$/**Dipamp**; **BPPM**, **259**	94, *S*	Hydrogenation of BOC-(*S*)-Ala-ΔPhe-(*S*)-Leu-OMe with H_2; double stereoselection	154
$C_{25}H_{22}O_2$	 $PhCH{=}CH\text{-}\underset{\substack{\mid\\ CH(COMe)COPh}}{CH}\text{-}Ph$	[(η^3-C_3H_5)PdCl]$_2$/**285**	87, *S*	Allylic alkylation of (*E*)-1,3-diphenyl-3-acetoxy-1-propene with NaCH(COMe)COPh	259
$C_{25}H_{29}NO_3Si$		[Rh(cod)Cl]$_2$/**Diop**	31, ***R***	Hydrosilylation of (3,4,5-MeO)$_3$-phenyl-3,4-dihydro-2*H*-pyrrole with H_2SiPh_2	213
$C_{25}H_{29}NO_4Si$	 $NpPhHSiO\text{-}\underset{\substack{\mid\\ Me}}{CH}\text{-}CONH\underset{\substack{\mid\\ CHMe_2}}{CH}COOMe$	[Rh(cod)Cl]$_2$/**Diop**	72, ***R***	Hydrosilylation of Me 2-oxo-propionyl-valinate with $H_2SiPhNp$	154
$C_{26}H_{24}O_4$	 $Ph\text{-}\underset{\substack{\mid\\ CH(COOMe)_2}}{CH}\text{-}CH{=}CPh_2$	[(η^3-C_3H_5)Pd(**Chiraphos**)]ClO$_4$; **Prophos**	86	Allylic alkylation of 1,1,3- and 1,3,3-triphenylprop-2-enyl acetate/ NaCH(COOMe)$_2$	250
$C_{26}H_{26}O_4S$	 $Me\text{-}\underset{\substack{\mid\\ CHCOOMe\\ \mid\\ SO_2C_6H_4(4\text{-}Me)}}{CH}\text{-}CH{=}CPh_2$	[(η^3-C_3H_5)Pd(**Chiraphos**)]ClO$_4$	65	Allylic alkylation of 4,4-diphenyl-3-buten-2-yl acetate with NaCH(COOMe)SO$_2$C$_6$H$_4$(4-Me)	250
$C_{26}H_{33}N_3O_6$	CBZ-Gly-(S)-Phe-(*S*)-Leu-OMe	[Rh(nbd)$_2$]ClO$_4$/**Dipamp**; **259**	93.4, *S*	Hydrogenation of CBZ-Gly-ΔPhe-(*S*)-Leu-OMe with H_2; double stereoselection	154

Table 3 (Contd)

Formula	Structure of Optically Active Compound	Enantioselective Catalyst	e.e. (%)	Reaction Type; Remarks	Ref.
$C_{26}H_{33}N_3O_6$	BOC-(*S*)-Phe-(S)-Phe-Gly-OMe	$[Rh(nbd)_2]ClO_4$/**Dipamp**; **BPPM**, **259**	93.4, *S*	Hydrogenation of BOC-(*S*)-Phe-ΔPhe-Gly-OMe with H_2; double stereoselection	154
$C_{27}H_{30}N_2O_3$	 $PhCH_2\text{-}\underset{HNCOMe}{CH}\text{-}CONH\underset{CH_2Ph}{C}HCH_2OR$	$[Rh(nbd)_2]ClO_4$/**BPPM′**; **Diop**, **259**	98.2, *S*	Hydrogenation of Ac-ΔPhe-β-phenylalaninol benzyl ether with H_2 ($R = CH_2Ph$)	154
$C_{28}H_{24}O_4S_2$	 $PhCH{=}CH\text{-}\underset{CH(SO_2Ph)_2}{CH}\text{-}Ph$	Pd-acetate/**292**	66	Allylic alkylation of 1,3-diphenyl allyl acetate with $NaCH(SO_2Ph)_2$	258
$C_{28}H_{27}NO_4Si$	 $NpPhHSiO\text{-}\underset{Ph}{CH}\text{-}CONH\underset{Me}{C}HCOOMe$	$[Rh(cod)Cl]_2$/**Diop′**	70, *S*	Hydrosilylation of Me 2-oxo-2-Ph-acetyl-alaninate with $H_2SiPhNp$	154
$C_{28}H_{34}N_4O_8$	Ac-(**R**)-Tyr(Ac)-(*R*)-Ala-Gly-(*S*)-Phe-OMe	$[Rh(nbd)_2]ClO_4$/**259**	99.2, *R*	Hydrogenation of Ac-ΔTyr(Ac)-(*R*)-Ala-Gly-(*S*)-Phe-OMe with H_2	154
$C_{28}H_{24}O_2$	 $1\text{-}NpCH{=}CH\text{-}\underset{CH(COMe)_2}{CH}\text{-}(1\text{-}Np)$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/**285**	92	Allylic alkylation of (*E*)-1,3-dinaphthyl-3-acetoxy-1-propene/$NaCH(COMe)_2$	259
$C_{28}H_{39}N_5O_5$	BOC-Gly-(S)-Phe-(*S*)-Leu-NHNHPh	$[Rh(nbd)_2]ClO_4$/**BPPM′**; **Dipamp**	85.8, *S*	Hydrogenation of BOC-Gly-ΔPhe-(*S*)-Leu-NHNHPh with H_2	154
$C_{29}H_{29}NO_4Si$	 $NpPhHSiO\text{-}\underset{Me}{CH}\text{-}CONH\underset{CH_2Ph}{C}HCOOMe$	$[Rh(cod)Cl]_2$/**Diop**	68, *R*	Hydrosilylation of Me 2-oxo-propionyl phenylalaninate with $H_2SiPhNp$; hydrolysis	154

$C_{29}H_{35}NO_7$	 $ACH{=}CH(CH_2)_3{-}\underset{NHCBZ}{CH}{-}COOMe$	[Rh(cod)**Dipamp**]BF_4	>98, *S*	Hydrogenation of (*E*/*Z*)-enamide; (*E*/*Z*) mixture 8:3; step in the chlamydocin synthesis	148
$C_{29}H_{39}N_3O_6S$	BOC-(*S*)-Phe-(S)-Phe-(*S*)-Met-OMe	$[Rh(nbd)_2]ClO_4$/**Dipamp**; **259**	92.4, *S*	Hydrogenation of BOC-(*S*)-Phe-ΔPhe-(*S*)-Met-OMe with H_2	154
$C_{30}H_{32}O_4$	 $Ar_2C{=}CH{-}\underset{CH(COOMe)_2}{CH}{-}Ph$	$[(\eta^3\text{-}C_3H_5)Pd($**Chiraphos**$)]ClO_4$; **Prophos**	64	Allylic alkylation of 1,1-bis(3,5-dimethylphenyl)-3-phenyl-prop-2-enyl acetate with $NaCH(COOMe)_2$	250
$C_{30}H_{41}N_3O_6$	BOC-(*S*)-Phe-(S)-Phe-(*S*)-Leu-OMe	$[Rh(nbd)_2]ClO_4$/**Dipamp**; **BPPM**, **259**	91.8, *S*	Hydrogenation of BOC-(*S*)-Phe-ΔPhe-(*S*)-Leu-OMe with H_2	154
$C_{34}H_{31}NO_4Si$	 $NpPhHSiO{-}\underset{Ph}{CH}{-}CONH\underset{CH_2Ph}{CH}COOMe$	$[Rh(cod)Cl]_2$/**Diop**′	82, *S*	Hydrosilylation of Me 2-oxo-2-Ph-acetylphenylalaninate with $H_2SiPhNp$; hydrolysis	154
$C_{44}H_{66}N_8O_{10}$	(BOC-Gly-(S)-Phe-(*S*)-Leu-$NH)_2$	$[Rh(nbd)_2]ClO_4$/**BPPM**′; **Dipamp**	97.6, *S*	Hydrogenation of (BOC-Gly-ΔPhe-(*S*)-Leu-$NH)_2$ with H_2	154

active diastereomers are formed). Optical rotations or other measures are used in case the optical purity of the product is unknown.

Column 5 begins with a key word characterizing the reaction type, followed by the names of substrates. It contains additional remarks when appropriate and permitted by the space available. When the name of a substrate is very long, only the relevant part is given. The reaction type and substrate name in combination with the formula of the product illustrate the catalytic synthesis under discussion. If different isomers of a product have been described, only that with the maximum optical induction is explicitly shown. The other isomers are mentioned in the remarks of column 5.

The last column cites the number of the reference. So for each optically active product in a given reference there is an entry in Table 3.

The optically active products in columns 1 and 2 invariably are the direct products of the enantioselective catalytic step. These direct products frequently have not been isolated but transformed into other compounds. Thus the direct product of the hydrosilylation of acetophenone with diphenylsilane, $Ph{-}CH(OSiHPh_2){-}Me$, entered in Table 3, usually is subsequently hydrolyzed to give the secondary alcohol 1-phenylethanol. Where possible, such additional transformations are indicated in the remarks of column 5.

Because of limited space, chemical yields, reaction conditions, and details of the work-up, though important information, could not be included in Table 3. Also, it was not possible to state whether an optically active product in column 2 is the only reaction product or is accompanied by side-products. For these details the reader is referred to the original papers. The results of papers 316–322, which are not available in the typical science languages, are not included in Tables 2 and 3. These papers are enumerated at the end of the list of references together with the reviews (323–344) that appeared in the report period in usually inaccessible journals or rare symposium volumes.

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Kinetic Resolution*

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*This chapter is dedicated to the memory of Professor H. Pracejus, who died on July 30, 1987 in Rostock (DDR).

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SYMBOLS AND ABBREVIATIONS

binap	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BSA	Bovine Serum albumin
C	Conversion
CPL	Circularly polarized light
DCT	Dicyclohexyl tartrate
DET	Diethyl tartrate
diop	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino-butane)
DIPT	Diisopropyl tartrate
DMT	Dimethyl tartrate
E	Biochemical stereoselectivity factor
e.e.	Enantiomeric excess
g	Anisotropy factor
h	Relative amount of uncoordinated substrate in a coordination process

HLADH	Horse liver alcohol dehydrogenase
K	Ratio of diastereomeric compounds
P	Enantiomeric excess of a starting material
PLE	Pig liver esterase
s	Stereoselectivity factor
TBHP	*t*-Butyl hydroperoxide
THF	Tetrahydrofuran
TMED	Tetramethylethylenediamine

I. INTRODUCTION

Resolution is a process closely connected with the beginnings of stereochemistry, since the first resolution was performed manually by Pasteur in 1848 (1) on racemic ammonium sodium tartrate (conglomerate modification). In 1858 Pasteur also discovered (2) the classical methods for resolution of a racemic mixture: combination with a chiral reagent and separation of the diastereoisomeric products or partial and enantioselective destruction by a chiral reagent (namely here an enzymatic system present in a microorganism). The latter experiment can be considered the first example of kinetic resolution. In 1858 Pasteur investigated fermentation of an aqueous solution of racemic ammonium tartrate by a *Penicillium glaucum* mold. He reisolated the remaining tartrate and found that it was optically active (levorotatory). This discovery was in a sense the end of the contribution of Pasteur to stereochemistry since he subsequently oriented his research toward microorganisms leading to major discoveries in biology.

Kinetic resolution can be defined as a process in which one of the enantiomer constituents of a racemic mixture is more readily transformed into a product than is the other (enantioselective reaction):

$$R \xrightarrow{k_R} P$$

$$S \xrightarrow{k_S} Q$$

Kinetic resolution occurs if $k_R \neq k_S$ and the reaction is stopped at some stage between 0 and 100% conversion. The ideal situation is that in which only one enantiomer reacts, for example, R ($k_R \gg k_S$), so that at 50% conversion a mixture of 50% S enantiomer and 50% product P is obtained. The difference in specific rate constants originates because the transformation is mediated by a chiral catalyst or a chiral reagent. The products P and Q can be achiral (identical or not) or chiral (with or without incorporation of a moiety derived from the chiral reagent). The nature of the products is irrelevant to the kinetic resolution process itself, where one looks mainly to the enantiomeric excess (e.e.) of recovered starting material. In the Pasteur experiment, microorganisms are the chiral reagent or catalyst, the products are metabolites of (R,R)-tartrate, while the recovered starting material is enantiomerically pure (S,S)-tartrate.

The first successful kinetic resolution by chemical means appears to be the report of Marckwald and McKenzie in 1899 (3) in which racemic mandelic acid was partially esterified by (−)-menthol under homogeneous conditions, leaving unreacted (−)-mandelic acid. Resolution of racemic mandelic acid with (−)-borneol was also observed (4). The first detailed kinetic study of such a resolution was given by Bredig and Fajans, who took as their example the asymmetric decarboxylation of camphorcarboxylic acid mediated by various alkaloids (5, 6). *Kinetic resolution* is usually performed in homogeneous medium and we discuss only this situation. Kinetic resolution essentially requires the partial transformation of a racemic mixture. This contrasts with classical methods of resolution which usually involve complete transformation of a racemic mixture into a mixture of diastereomers. Moreover, we do not include processes in which enantiomers are obtained (i) by separation of a mixture of diastereomers followed by a cleavage and (ii) by selective cleavage of a mixture of diastereomers (either present in equimolar amounts or in some ratio resulting from an epimerization equilibrium).

Chromatographic separations of mixtures of enantiomers on a chiral stationary phase or differential transport through liquid membranes with the aid of a chiral phase-transfer agent are also not considered.

Kinetic resolution is basically linked to kinetics. We shall give a picture of the quantitative aspects of kinetic resolution through various kinetic scenarios (including enzymatic reactions and polymerizations). The preparative aspects of kinetic resolutions are emphasized in Sect. III, while Sect. IV is devoted to the applications of kinetic resolution to some problems of mechanistic interest.

No extended review of kinetic resolutions is presently available. However, many of the results obtained before 1975 are reported in ref. 6.

II. KINETIC ASPECTS

It is important to correlate the e.e.'s of the partners of a kinetic resolution (either the reactants or the products when the latter are chiral, or both) as a function of reaction time in various kinetic schema. Such calculations were performed a long time ago, for example, by Fajans (5, 6) and Kuhn (7), and more recently by Mislow (8). In this era of computers, easy computation of complex systems is now possible, giving theoretical curves expressing the evolution of e.e.'s or concentrations of various species as the reaction is going on. Some examples from the last two decades follow.

A. Kinetics

A kinetic resolution can be approximated by the set of reactions [1] and [2] where B* stands for a chiral reagent:

$$R + \mathrm{B}^* \xrightarrow{k_R} \mathrm{P} \qquad [1]$$

$$S + \mathrm{B}^* \xrightarrow{k_S} \mathrm{Q} \qquad [2]$$

If B* is achiral and if there is instead a chiral catalyst, the latter does not appear in eqs. [1] and [2].

Let us assume that the reaction starts from 1 mol of racemic mixture ($[R]_0 = [S]_0 = 0.5$ at time $t = 0$) and that conversion is equal to C ($0 < C < 1$) at time t. The amount of recovered material at time t is $[R] + [S] = 1 - C$, its enantiomeric excess is e.e. $= ([S] - [R])/([S] + [R])$ (e.e. > 0 if $k_R > k_S$, giving enrichment in the S enantiomer). By combining the two relations, eqs. [1] and [2], with the definition of e.e., the amounts of R and S enantiomers may be calculated:

$$[S] = \frac{(1-C)(1+\text{e.e.})}{2}, \qquad [R] = \frac{(1-C)(1-\text{e.e.})}{2}$$

The success of the kinetic resolution for a given conversion C is expressed by the e.e. value for unreacted substrate $R + S$. This value is directly related to C and to the stereoselectivity factor $\mathbf{s} = k_R/k_S$. The relation between e.e., C and $\mathbf{s}$ depends on the kinetics. Let us assume a commonly encountered case where reactions [1] and [2] are pseudo-first-order with respect to R and S, and B* is present in large excess or is a chiral catalyst.

Then

$$\frac{\mathrm{d}[R]}{\mathrm{d}t} = -k_R[R], \qquad \frac{\mathrm{d}[S]}{\mathrm{d}t} = -k_S[S]$$

After integration and combination of these equations, the stereoselectivity factor $\mathbf{s}$ is given by

$$\mathbf{s} = \frac{\ln([R]/[R_0])}{\ln([S]/[S_0])} = \frac{\ln 2[R]}{\ln 2[S]} \qquad [3]$$

Hence

$$\mathbf{s}=\frac{\ln[(1-C)(1-\text{e.e.})]}{\ln[(1-C)(1+\text{e.e.})]} \qquad [4]$$

By performing kinetic resolutions to several different extents of conversion and by measuring the e.e.'s of recovered starting material, it becomes possible to calculate the stereoselectivity factor $\mathbf{s}=k_R/k_S$, which is independent of the conversion. Fundamental eq. [4] also allows us to express e.e. as a function of **s** and C by numerical computations. Another equation to calculate **s**, equivalent to [4] has been given by Danishefsky and Cain (9). Typical curves (Figures 1–6) describing the efficiency of resolution as a function of conversion or time are discussed later.

The quantity $[S]-[R]$ is time dependent:

$$[S]-[R]=0.5[\exp(-k_S t)-\exp(-k_R t)] \qquad [5]$$

This quantity is equal to zero when $t=0$ ($[R]_0=[S]_0=0.5$) as well as at $t\rightarrow\infty$. This means that the excess of the major enantiomer (when expressed by $[S]-[R]$) achieves a maximum value at an intermediate time $t_{\max}$. This time corresponds to the situation in which the rates of destruction (not the specific rates) of both enantiomers become equal ($k_S[S]=k_R[R]$). When $t<t_{\max}$, the S enantiomer has accumulated; however, S is the fast-reacting species for $t>t_{\max}$. The time $t_{\max}$ corresponding to inversion of rates can easily be found by deriving eq. [5]: $t_{\max}=k_R/k_S=\mathbf{s}$. At $t_{\max}$, $[S]/[R]=k_R/k_S=\mathbf{s}$, hence e.e. $=(\mathbf{s}-1)/(\mathbf{s}+1)$.

Sometimes the products arising from a kinetic resolution are themselves chiral. Let us assume that P and Q in reactions [1] and [2] are enantiomers (labeled R' and S', respectively). The enantiomeric excess of the product (e.e.$'$) is defined by e.e.$'=([R']-[S'])/([R']+[S'])$. Since R' is derived from the fast-reacting (R) enantiomer, $[R']>[S']$ and consequently e.e.$'>0$. Because $[R']+[S']=C$, it is easy to modify eq. [3] into eq. [6], which gives the stereoselectivity factor **s** as a function of e.e.$'$ and C:

$$\mathbf{s}=\frac{\ln[1-C(1+\text{e.e.}')]}{\ln[1-C(1-\text{e.e.}')]} \qquad [6]$$

The material balance imposes a relationship between C, e.e., and e.e.$'$. After recalling that 0.5 mol of R enantiomer is distributed between the chiral product and the recovered starting material, relation [7], which is independent of **s**, may be derived:

$$\frac{\text{e.e.}}{\text{e.e.}'} = \frac{C}{1-C} \qquad [7]$$

If the competing reactions [1] and [2] are second-order (first-order with respect to R or S and first-order with respect to B), it is also possible to calculate the relation between the stereoselectivity factor $\mathbf{s} = k_R/k_S$, e.e., and C. Once again, this relationship is given by eq. [4], which is valid for all kinetic resolutions involving the set of homocompetitive reactions [1] and [2] where the reaction is first-order with respect to R or S, and any order with respect to B.

B. Evolution of e.e. with Time or Conversion

If one assumes pseudo-first-order kinetics and an irreversible reaction, it is easy to compute the concentration of the components of a kinetic resolution as a function of time.

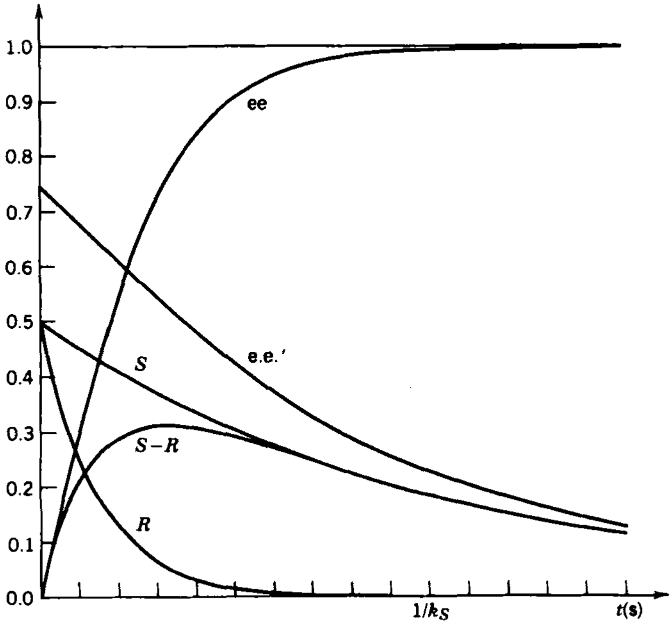


Figure 1. Pseudo-first-order kinetic resolution with time as parameter. Computed curves for relative rate **s** = 7.

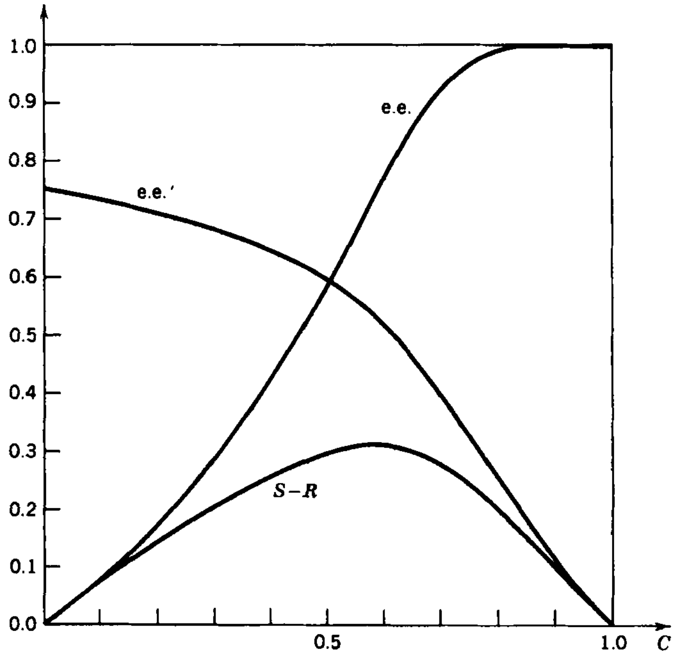


Figure 2. Pseudo-first-order kinetic resolution with conversion C as parameter. Computed curves for relative rate $\mathbf{s}=7$.

1. Pseudo-first-order reactions: Figures 1 and 2 show the evolution with time t or conversion C of the following quantities: $[R]$, $[S]$, $[S]-[R]$, e.e., and e.e.' when $\mathbf{s}=7$. At time $t \rightarrow 0$, e.e.$_0=0$ while e.e.$'_0=(\mathbf{s}-1)/(\mathbf{s}+1)$. At time $t \rightarrow \infty$, e.e.$\rightarrow 1$ while e.e.$'\rightarrow 0$.

It is a *general conclusion* (even for second-order kinetic resolutions) that the enantiomeric excess of starting material, e.e., *increases* with reaction time or conversion while the enantiomeric excess of the product, e.e.', (if the latter is chiral) continuously *decreases.*

When kinetic resolution (with a given **s** value) is used for preparative purposes, one wants to maximize both the amount of recovered material and its e.e. However, as shown in Figures 1 and 2, it is impossible to fulfil simultaneously both of these requirements: one has to decide whether the main aim is to get a product with a very high enantiomeric purity at the expense of the yield (C close to 1), or if one needs a substantial amount of optically active material (at the expense of its enantiomeric purity). A common compromise is to achieve conversion close to 50% ($C=0.5$). Some specific cases are discussed later. It is possible to find in the literature several papers in which curves or data tables are computed for solving some specific problems. Some examples are detailed below.

In 1958 Mislow et al. (8) studied the kinetic resolution of a ketone with axial chirality, the carbonyl group lying on the C_2 symmetry axis. A Meerwein–Ponndorf reduction was performed on the ketone with an excess of (+)-pinacolyl alcohol. There was an excellent fit between the computed and observed enantiomeric excesses (e.e. and e.e.′) as function of time for $\mathbf{s} = 2.2$ (Figure 3).

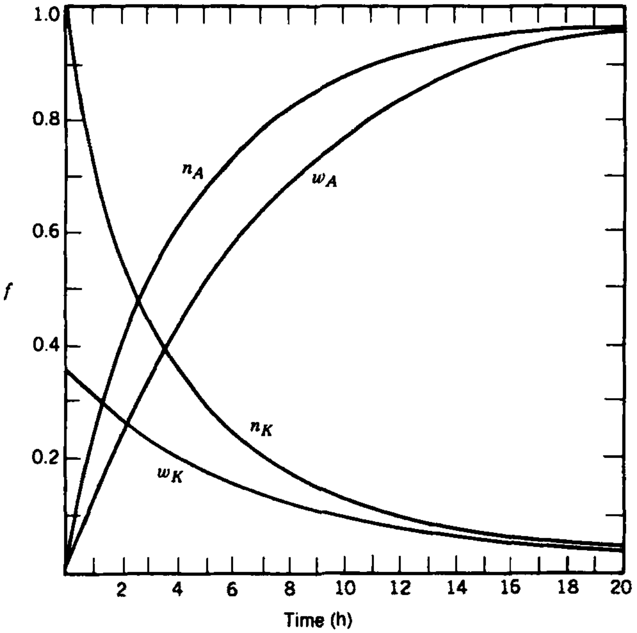


Figure 3. Calculated fractional (f) enantiomeric purities (W_A and W_B) and mole fractions (n_A and n_B) in a kinetic resolution of pseudo-first-order reactions (relative rate 2.2). A and K represent the product and the starting material, respectively. The reagent is an excess of (+)-pinacolyl alcohol. Reprinted with permission from Newman et al., *J. Am. Chem. Soc. 80*, 465–472. Copyright 1958 American Chemical Society.

The photochemical resolution of racemic substrates under the influence of circularly polarized light (which replaces chiral reagent B* or the chiral catalyst in eqs. [1] and [2]) was discussed by Kagan et al. (10) in relation to the anisotropy factor $\mathbf{g}$ defined by Kuhn (7) as $\Delta\varepsilon/\varepsilon = (\varepsilon_R - \varepsilon_S)/\frac{1}{2}(\varepsilon_R + \varepsilon_S)$. The process is well approximated by a set of two pseudo-first-order competitive reactions where k_R and k_S are proportional to ε_R and ε_S, respectively. In

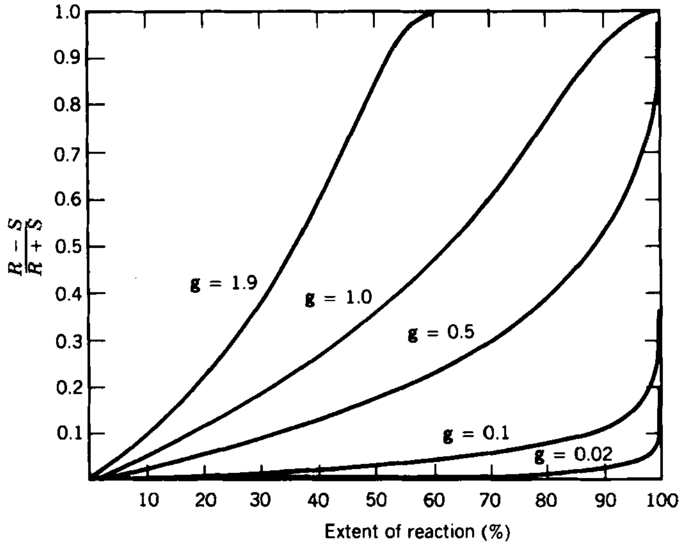


Figure 4. Evolution of e.e.% of recovered material as a function of anisotropy factor **g** and the extent of reaction. Reprinted with permission from Balavoine et al., *J. Am. Chem. Soc. 96*, 5152–5158. Copyright 1974 American Chemical Society.

Figure 4 computed curves have been drawn for various values of the **g** factor ($\mathbf{g}=2(k_R-k_S)/(k_R+k_S)=2(\mathbf{s}-1)/(\mathbf{s}+1)$) taken as the stereoselectivity index of the kinetic resolution. The **g** factors for organic molecules are usually quite small in magnitude, 10^{-3} to 0.2 corresponding to $\mathbf{s}<1.1$. Nevertheless, appreciable enantiomeric excess can be expected for the recovered material. This point is discussed in Sect. IV.

In kinetic resolutions involving chiral reagents or catalysts, the ratio of pseudo-first-order rate constants **s** gives a better indication of the efficiency than does the **g** factor. In 1976, Meurling et al. (11) gave an analysis of a reaction involving a kinetic resolution in the rearrangement of racemic 1-methylindene into achiral 3-methylindene under the influence of hydroquinidine ($\mathbf{s}=3.2$). A table of data was provided (Table 1) which allows one to know the extent of reaction C required for recovering starting material with e.e. = 99% in a kinetic resolution (pseudo-first-order conditions).

In 1981 Sharpless et al. (12) published computed curves (Figure 5) which visualize better the evolution of e.e. as a function of conversion for various values of **s**. Sharpless epoxidation allows very efficient kinetic resolution of allylic alcohols ($\mathbf{s}<138$) and is discussed in Sect. III. The same types of curves as those shown in Figure 5 were obtained by Sih et al. (13) in 1982 for enzymatic kinetic resolutions (see Sect. II-E).

Table 1
Extent of Reaction $C(\%)$ and Stereoselectivity Factor **s** ($\leqslant 10$) Required for Obtaining Recovered Material with Enantiomeric Composition of 99% e.e. in Kinetic Resolution of a Racemic Mixture[a]

s	*C*	**s**	*C*	**s**	*C*	**s**	*C*
1.5	99.999	2.0	99.7	2.8	97.3	5.0	86.6
1.7	99.97	2.2	99.4	3.0	96.4	7.0	79.2
1.8	99.93	2.4	18.9	3.5	94.0	10.0	72.1
1.9	99.86	2.6	98.2	4.0	91.3		

[a] From ref. 11.

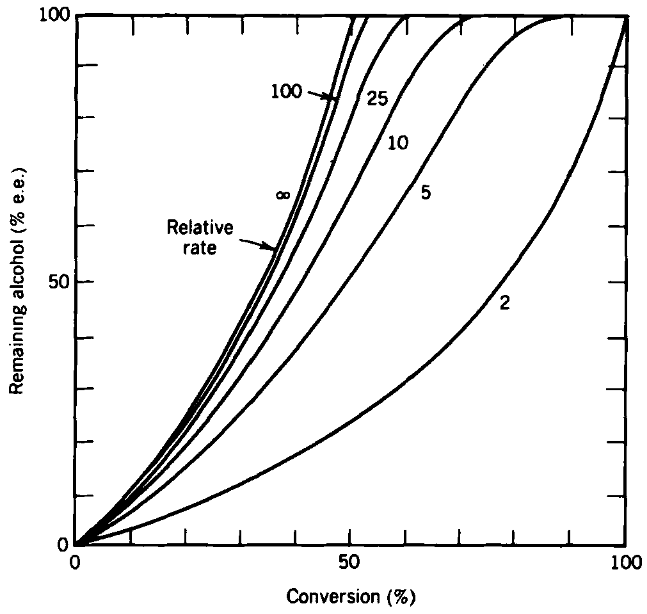


Figure 5. Dependence of e.e.% of recovered material on **s** factor (relative rate) and on conversion. Reprinted with permission from Martin et al., *J. Am. Chem. Soc. 103*, 6237–6240. Copyright 1981 American Chemical Society.

2. There are few reports of kinetic resolutions dealing with second-order reactions. The general trends (increase of e.e. and decrease of e.e.′ with the extent of reaction *C*) are preserved when going from first-order to second-order kinetics (14). A detailed kinetic analysis of a second-order kinetic

resolution in the case of racemic sulfoxides by reduction with chiral poly (*N*-alkyliminoalanes) has appeared recently (15).

As demonstrated above, the stereoselectivity factor **s** is expressed by eq. [4] when the reaction is first-order with respect to *R* or *S* and of any order with respect to chiral reagent B* (or to achiral reagent B in the presence of a chiral catalyst). Thus the curves of Figure 5 and the data in Table 1 apply. If the reaction is second-order exclusively with respect to *R* or *S* (and not with respect to *R* and *S*) and of any order with respect to B*, it is easy to establish that the stereoselectivity factor **s** is related to *C* and e.e. by the equation

$$\mathbf{s}=\frac{1+\text{e.e.}}{1-\text{e.e.}}\times\frac{1+(1-C)(1-\text{e.e.})}{1+(1-C)(1+\text{e.e.})}$$

This equation is equivalent to the expression obtained in kinetic resolutions involved in asymmetric polymerizations when the consumption of monomer is second-order (16), (see Sect. II-K). When $C \to 1$, the limit of e.e. is $(\mathbf{s}-1)/(\mathbf{s}+1)$. The difference with kinetic resolutions that are first-order with respect to substrate is that in the second-order cases it is not possible to reach

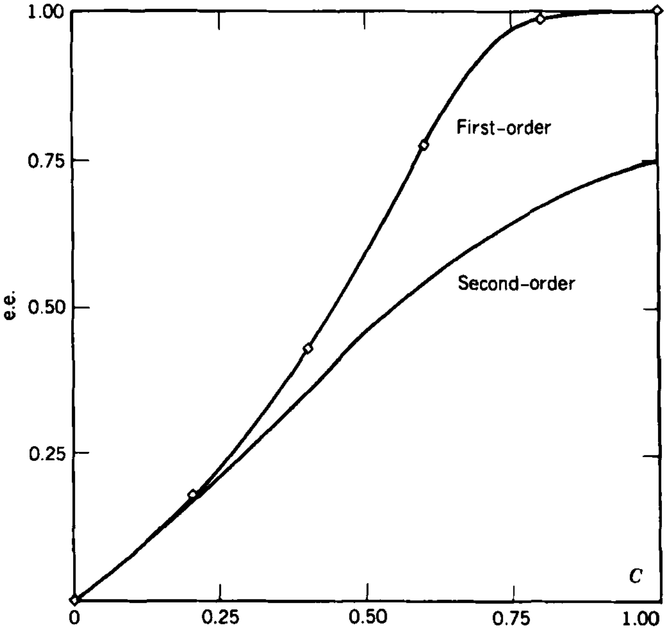


Figure 6. Comparison between kinetic resolutions (**s** = 7) involving homocompetitive reactions of either first-order or second-order with respect to substrate.

100% e.e. for high conversion since $(\mathbf{s}-1)/(\mathbf{s}+1)$ remains less than 1 unless $\mathbf{s}\to\infty$. However, if one can find chiral systems giving a high **s** factor, the limiting e.e. can be quite high, for example, $\mathbf{s}=100$ and $C\to 1$ give e.e.→98%. In Figure 6, computed curves ($\mathbf{s}=7$) show the different trends between first-order and second-order (with respect to substrate) kinetic resolutions. The two types of curves have been experimentally confirmed (16).

C. Synthetic Applications

As already stated, kinetic resolution processes can be useful for preparative purposes if it is possible to maximize the amount of recovered material $(1-C)$ and e.e.

Equation [4] and the curves in Figures 1–5 clearly show that one can obtain as high an e.e. as desired if important losses can be tolerated. To recover enough material of high e.e. from a racemic mixture, one needs to select reactions with a selectivity factor **s** that is large enough. The data of Table 1, calculated for small or moderate **s** factor (<10), show that to obtain a 20% yield of a recovered material with 99% e.e. from a racemic mixture, it is necessary to find a chiral reagent or catalyst giving a stereoselective reaction with an **s** factor close to 7. A 20% yield is not unreasonable since we must recall that 50% is the maximum yield expected in a perfect kinetic resolution.

Most of the chemical kinetic resolutions described in the literature involve **s** factors smaller than 10. However, quite recently very efficient chiral reagents and catalysts have been discovered. For example, with the Sharpless reagent the kinetic resolution of racemic allylic alcohols may be carried out with very high efficiency (12). In Table 2 some **s** values (between 10 and 500)

Table 2
Extent of Reaction *C* (%) and Stereoselectivity Factor **s** (≤ 1000) Required for Obtaining Recovered Material with Enantiomeric Composition of 99% e.e. in Kinetic Resolution of a Racemic Mixture

s	*C*	**s**	*C*
10.0	72.1	200	51.1
20	61.9	300	50.6
50	54.9	500	50.3
100	52.3	1000	50.01
150	51.5		

are given together with the corresponding conversion needed for attaining e.e.'s of 99% when starting from a racemic mixture. For **s** values higher than 150, the conversion is close to 50%. Clearly the process is synthetically useful and now competitive with enzymatic resolutions.

D. A Route to Enantiomerically Pure Compounds

Kinetic resolution is a way to achieve the preparation of optically pure compounds by taking advantage of two parameters: the extent of reaction C and the stereoselectivity factor **s**. As early as 1930 Kuhn (7) stated that, in principle, high e.e.'s should be attained in kinetic resolutions with low **s** factors, just by carrying out the reactions almost to completion. This was experimentally confirmed in photoresolutions of racemic ketones with circularly polarized light (10).

In 1975, Horeau discussed the use of kinetic resolution techniques for achieving very high e.e.'s for a compound that is only partially resolved (17). Let us call e.e. and E.E. the initial and the final enantiomeric excesses of a compound, respectively. If the reaction is first-order or pseudo-first-order with respect to the partially resolved substrate (and of any order with respect to a chiral reagent), the kinetics of homocompetitive reactions applies as above. Horeau established that e.e., E.E., and C are related by eq. [8]:

$$(1-C)^{\mathbf{s}-1}=\frac{1-\text{E.E.}}{1-\text{e.e.}}\times\frac{(1+\text{e.e.})^{\mathbf{s}}}{(1+\text{E.E.})^{\mathbf{s}}} \qquad [8]$$

In this equation $\mathbf{s}>1$ $(k_R>k_S)$, and e.e. and E.E. are defined by the ratio $([S]-[R])/([S]+[R])$ since the S isomer is the slow-reacting species. By way of example, eq. [8] was used by Horeau to calculate the stereoselectivity factor and the percentage of conversion necessary to reach 99.9% e.e. (close to the limit of sensitivity of measurement) starting from a compound with e.e. $=90$ or 95%. It is interesting to see (Figure 7) that with the moderate rate ratio $\mathbf{s}=10$, less than 50% destruction of starting material suffices to obtain an essentially enantiomerically pure substance. Experimental verification of eq. [8] was obtained by Horeau in the case of esterification of partially resolved alcohols with a chiral anhydride.

In 1977 Ugi et al. (18) published a very detailed paper on chemical selectivity in kinetically controlled systems of parallel reactions. General equations and data tables were given, including the particular case of kinetic resolution. Because of its mathematical presentation, this paper has seldom been quoted by people working on chirality. The applicability of kinetic resolution for the chemical purification of partially resolved mixtures (for example, as derived from asymmetric syntheses) was also illuminated by

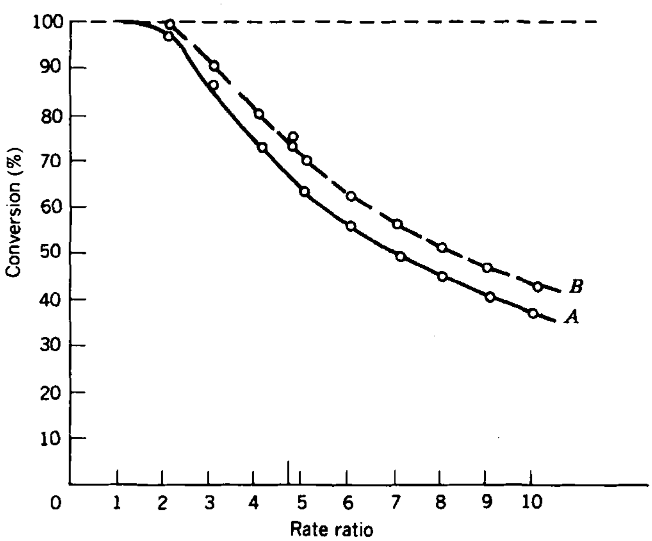


Figure 7. Percentage conversion of a mixture of enantiomers required to change its e.e. from 95 (curve *A*) or 90 (curve *B*) to 99.9%. Reprinted with permission from Horeau, *Tetrahedron* **1975**, *31*, 1307–1309.

various calculations. In ref. 18, tables are given that allow one to know the maximum amount of purified compound that may be obtained in a kinetic resolution (for a given **s** value) so as to reach an unlimited enantiomeric purity (99.8–99.998%), starting from a given e.e. value. In Table 3 we have

Table 3

Percent $(([S]/[S_0]) \times 100)$ of purified *S* enantiomer (e.e. = 99.8%) Computed with Given Values of Percent Initial Enantiomeric Excesses (e.e.%) and Stereoselectivity Factor $\mathbf{s} = k_R/k_S$[a]

	s							
e.e.%	2.5	5	10	20	40	80	160	320
0	1.1	17.8	46.5	69.6	83.8	91.7	95.8	97.9
40	1.8	22	51.1	72.7	85.7	92.7	96.3	98.2
60	2.6	25.2	54.2	74.8	86.9	93.3	96.6	98.3
80	4.4	30.9	59.3	78.1	88.7	94.3	97.1	98.6
96	13.4	47.1	71.6	85.4	92.6	96.3	98.2	99.1
98	21.5	56.2	77.4	88.6	94.3	97.2	98.6	99.3

[a] From ref. 18.

reproduced with the conventions used here the numbers given in ref. 18 for evaluating the yield of the recovered major enantiomer (E.E. = 99.8%) starting from an e.e. between 0 and 98%. It is obvious that with high stereoselectivity factors (**s** > 80), there is a good prospect of recovering the major enantiomer with an excellent yield. For example, a mixture of enantiomers with an enantiomeric excess of 40% (*S* configuration) can be converted by kinetic resolution to an *S* enantiomer of 98.8% e.e. in 92.7% yield (with respect to the initial amount of *S* enantiomer in the starting material), if the stereoselectivity factor is 80. With **s** = 5, only 1.8% of *S* enantiomer with 98.8% e.e. will be reisolated.

The Sharpless reagent for the asymmetric epoxidation of allylic alcohols is highly efficient in the kinetic resolution of racemic allylic alcohols (12), with selectivity factors much larger than 10. Sharpless has pointed out that eq. [4] shows that any degree of enantiomeric purity can be obtained without extensive conversion because of the high values of **s**. For example, $CH_2{=}C(Me)CH(OH)CH_2CH_2CH_2CH_3$ is epoxidized by the Sharpless reagent ($Ti(OiPr)_4$/diisopropyl tartrate/*t*-BuOOH) with a stereoselectivity factor **s** = 138. Equation [4] indicates that for 60% conversion ($C = 0.60$) the enantiomeric excess of remaining allylic alcohol is calculated to be 99.99999999999%! These results led Sharpless to speculate that such chemical kinetic resolutions could be close to removing "the last molecule" of the fast-reacting enantiomer.

As already stated by Horeau (17), it is possible to prepare a sample of an enantiomeric excess as high as desired (and far beyond the accuracy of conventional methods of measurement) just by knowing the **s** factor and by carrying out the kinetic resolution on a sample of a given e.e. up to a calculated extent of conversion.

E. Enzymatic Reactions

A quantitative analysis of biochemical kinetic resolutions of enantiomers was developed in 1984 by Sih et al. (19). The equations and data tables of Sect. II-A apply to enzymatic systems although, as in all systems involving asymmetric catalysis, the kinetic scheme is quite complicated. The authors (19) approximated the kinetics of enzymatic reactions by means of a simple three-step mechanism which assumes that the reaction is irreversible and that product inhibition is absent (eq. [9]; *E* = enzyme).

$$\begin{aligned} &R+\mathrm{E} \underset{k_2}{\overset{k_1 R}{\rightleftharpoons}} \mathrm{E}\text{–}R \xrightarrow{k_3} \mathrm{E\text{–}P} \xrightarrow{k_4} \mathrm{E+P} \\ &S+\mathrm{E} \underset{k_2'}{\overset{k_1 S}{\rightleftharpoons}} \mathrm{E}\text{–}S \xrightarrow{k_3'} \mathrm{E\text{–}Q} \xrightarrow{k_4'} \mathrm{E+Q} \end{aligned} \qquad [9]$$

Steady-state kinetics applied to [9] gives

$$\frac{v_R}{v_S}=\frac{V_R}{V_S}\times\frac{k_S}{k_R}\times\frac{[R]}{[S]} \qquad [10]$$

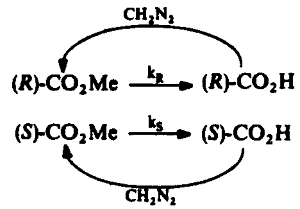
where v_R and v_S are partial reaction rates, while V_R, k_R and V_S, k_S denote maximal velocities and Michaelis constants of the fast- and slow-reacting enantiomers, respectively.

Integration of eq. [10] and further transformation using the conventions of Sect. II-A leads to eq. [11].

$$\mathbf{E}=\frac{V_R k_R}{V_S k_S}=\frac{\ln[(1-C)(1-\text{e.e.})]}{\ln[(1-C)(1+\text{e.e.})]} \qquad [11]$$

Equation [11] is formally identical to eq. [4]. The biochemical stereoselectivity factor **E** is equivalent to the chemical stereoselectivity factor **s**, although (19) **E** depends on the ratio of the enzymatic specificity constants (V/K). As far as the **E** factor is concerned, all the conclusions obtained with **s** are retained, such as quantitative predictions relating the extent of conversion of a racemic substrate and the enantiomeric composition of recovered material and of chiral products. Experiments (19) nicely confirm the validity of eqs. [4], [6], and [11]. For example, racemic *erythro*-methyl 2,4-dimethyl-3-hydroxypent-4-enoate was hydrolyzed by *gliocladium roseum* and the percent enantiomeric excess of ester and of the corresponding acid (reaction product) were plotted against percent conversion. Curves similar to those in Figure 1 were obtained, giving an excellent fit with calculated curves for **E** = 20.

The hydrolysis of racemic esters catalyzed by enzymes is a quite common process. Sih et al. (19) proposed to isolate the acidic fraction and to reesterify it. A new kinetic resolution process with the same hydrolytic enzyme can give high e.e.'s for the ester if the conversion extent is properly controlled:



If (R)-CO_2Me is the fast-reacting species, the first enzymatic kinetic resolution (**E** stereoselectivity) will accumulate (S)-CO_2Me and (R)-CO_2H (with e.e.$_0$ and e.e.$'_0$, respectively, for conversion C_0). The relative amounts C and

$(1-C)$ of (S)-CO_2H and (R)-CO_2Me are equal to the inverse ratio of their enantiomeric purities (eq. [7]). After separation and esterification of the acid, the recycled substrate mostly consists of (R)-CO_2Me (with $\text{e.e.}'_0$). A new enzymatic hydrolysis with a conversion C will produce RCO_2H (of e.e.′) and unreacted RCO_2Me. Equation [11] becomes eq. [12], which interrelates $\text{e.e.}'_0$, e.e.′, and C:

$$1-C\left(\frac{1-\text{e.e.}'}{1+\text{e.e.}'_0}\right)=\left[1-C\left(\frac{1-\text{e.e.}'}{1-\text{e.e.}'_0}\right)\right]^E \qquad [12]$$

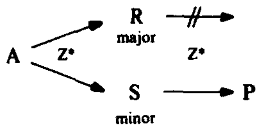
This recycling method (20) allows one to obtain chiral acids of high e.e. (e.g., arbitrarily set at 98%) if the maximum conversion C is calculated by means of eq. [12], once **E** is measured in a first kinetic resolution.

F. Combination of Asymmetric Synthesis and Kinetic Resolution

Asymmetric synthesis and kinetic resolution can be interrelated in several ways: (i) A chiral reagent or catalyst is first used to perform an asymmetric synthesis and then is reused to carry out a kinetic resolution on the partially resolved product obtained in the asymmetric synthesis. Enhancement of the e.e.'s are observed in favorable cases; (ii) a racemic or partially resolved compound bearing a prochiral center reacts with a chiral reagent or catalyst. A new asymmetric center is created and kinetic resolution can occur simultaneously if the reaction is incomplete.

1. Enhancement of the e.e. of a Product Formed During an Asymmetric Synthesis

It seems very attractive to use the same chiral auxiliary Z* to direct an asymmetric synthesis and then to control the destruction of the minor enantiomer in a subsequent resolution step. A one-pot reaction would be ideal. A related situation was found (18) in the Ugi–Passerini reaction (4-component condensation), which allows one to prepare optically active dipeptides or analogs (Figure 8). In that system Z* is a chiral ferrocenyl moiety. The chiral auxiliary is still present in the diastereomeric products A and A′ of the asymmetric condensation. The major diastereomer A can be



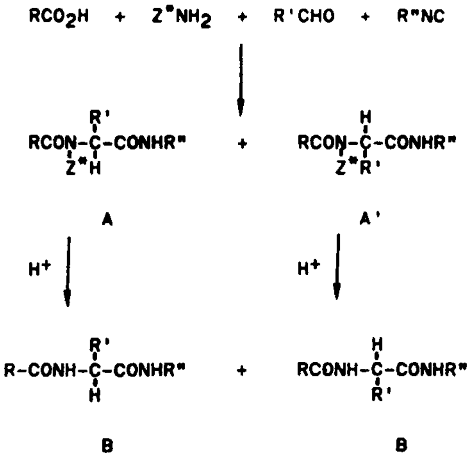

RCO2H + Z*NH2 + R'CHO + R"NC
RCON-C-CONHR" (R', Z*, H)
+
RCON-C-CONHR" (H, Z*, R')
A
A'
H+
H+
R-CONH-C-CONHR" (R', H)
+
RCONH-C-CONHR" (H, R')
B
B

Figure 8. Four-component reaction (18).

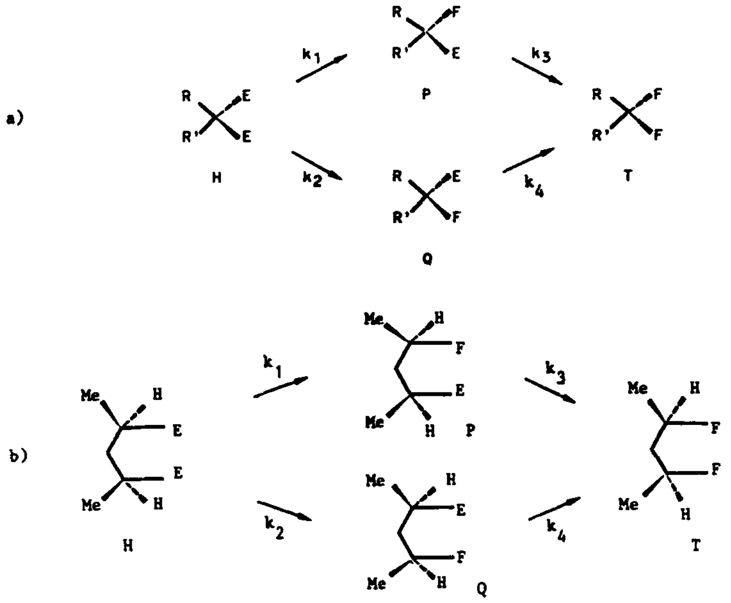
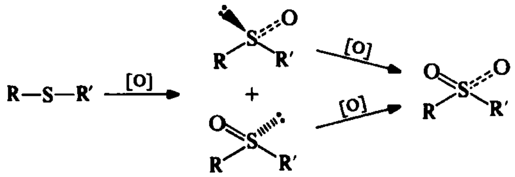

a)
R
E
R'
E
H
k1
k2
R
F
R'
E
P
R
E
R'
F
Q
k3
k4
R
F
R'
F
T
b)
Me
H
E
E
Me
H
H
k1
k2
Me
H
F
E
Me
H
P
Me
H
E
F
Me
H
Q
k3
k4
Me
H
F
F
Me
H
T

Figure 9. Use of difunctional prochiral substrates in asymmetric synthesis combined with kinetic resolution (E, functional group).

easily purified by a controlled acidolysis of the minor diastereomer A′. After separation A is quantitatively transformed by acidolysis into diamide B of very high e.e. Another scheme that concerns difunctional prochiral substrates is depicted in Figure 9.

An example is the asymmetric oxidation of prochiral sulfides to chiral sulfoxides. An overoxidation ultimately leads to achiral sulfones:



Sugimoto et al. (20) studied the oxidation of aromatic alkyl sulfides to sulfoxides by means of $NaIO_4$ or H_2O_2 in the binding domain of bovine serum albumin (BSA). An e.e. of 78% was obtained in the asymmetric synthesis of isopropyl phenyl sulfoxide (*R* configuration) with H_2O_2. Kinetic resolution of the same but racemic sulfoxide gave 18% e.e. (*R* configuration) for 50% completion of oxidation. This experiment means that (*S*)-sulfoxide was consumed. Then some overoxidation of isopropyl phenyl sulfide was allowed to take place: when the yield of sulfoxide is 47%, its e.e. is 93%. By this one-pot method several phenyl alkyl sulfoxides were obtained in yields close to 50% with e.e.'s higher than 90%. Interestingly, alkyl *p*-tolyl sulfoxides behave differently in the binding site of BSA: (*R*)-sulfoxides are again produced by oxidation of sulfides but they are oxidized faster than (*S*)-sulfoxides. Consequently, the combination of asymmetric synthesis and kinetic resolution is not beneficial for alkyl *p*-tolyl sulfides in the presence of the oxidant system H_2O_2/BSA; there is a decrease of the e.e.'s of the sulfoxides.

Recently, Sih et al. (19) discussed the enzyme-catalyzed hydrolysis of prochiral diesters to chiral monoesters (Figure 9*b*, E = OAc, F = OH). The same enzyme can be used to go to the achiral diol stage. One can envisage that the enantioselectivity ($k_1 > k_2$) is more or less retained in the second step, allowing preferred reaction on one of the E groups again ($k_4 > k_3$). If this is the case, the enantiomeric excess of the monoester can very much increase, just by a limited overhydrolysis which will eliminate the minor enantiomer. Calculations show clearly the advantages of this method. The authors (19) were able to arrive at the quantitative expressions for the concentrations of H, P, Q, and T (Figure 9) at any extent of conversion as a function of the pseudo-first-order rate constants k_1–k_4. Experiments nicely confirmed the predictions. This strategy was applied to the preparation of the monoacetates shown in Figure 10.

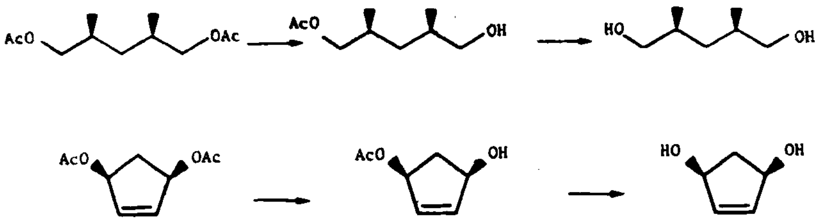

AcO
OAc
AcO
OH
HO
OH
AcO
OAc
AcO
OH
HO
OH

Figure 10. Synthesis of chiral monoacetates with e.e. enhancement (enzymatic hydrolysis with PLE) (19).

Schreiber et al. (21) recently discussed reactions occurring in systems related to those depicted in Figure 9 where E groups were prochiral themselves (e.g., C = C or C = O double bonds). If the asymmetric reagent attacks a double bond, four stereoisomeric products can be formed (Figure 11). The

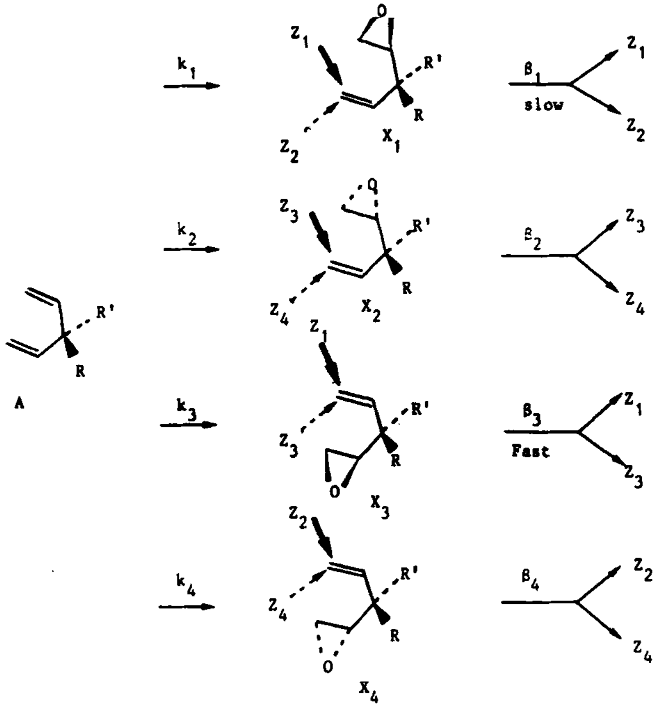

R'
R
A
k_1
k_2
k_3
k_4
O
Z_1
R'
R
Z_2
X_1
O
Z_3
R'
R
Z_4
X_2
Z_1
R'
Z_3
R
O
X_3
Z_2
R'
Z_4
R
O
X_4
β_1
slow
Z_1
Z_2
β_2
Z_3
Z_4
β_3
Fast
Z_1
Z_3
β_4
Z_2
Z_4

Figure 11. Asymmetric synthesis (epoxidation as an example) of $X_1 (k_1 > k_3)$, combined *in situ* with a kinetic resolution by the same chiral reagent ($\beta_3 > \beta_1$) (21). $Z_1 \cdots Z_4$ represent the various stereoisomeric diepoxides.

formation of Y_1 as major product, for example, in asymmetric epoxidation, is the result of a double stereoselection: an enantiotopic group differentiation is combined with a diastereotopic face differentiation (since $R \neq R'$ the four faces of the substrate are different). The kinetics of the system can be described as follows:

$$\mathrm{A} + \mathrm{B} \xrightarrow{k_i} \mathrm{X}_i, \qquad i = 1\text{–}4$$

$$\mathrm{X}_i + \mathrm{B} \xrightarrow{k_i} \mathrm{Z}_i, \qquad i = 1\text{–}4$$

where B is a chiral reagent, X_1 and X_3 (and X_2 and X_4) are enantiomers. The ratio X_1/X_3 (thus the e.e.) varies with time since destruction of X_i occurs by the second addition on the remaining double bond. If $k_1 > k_2$, k_3, and k_4, the major product will initially be X_1. If the chiral reagent gives a strong face differentiation (large k_1/k_2) it will react faster with the face of X_3 which best recalls the steric situation of the transition state leading to X_1.

One can expect that conclusion if the rates of the second addition are not very much influenced by the first addition [$\beta_1 = \beta_2 \approx (k_3 + k_4)$ and $\beta_3 = \beta_4 \approx (k_1 + k_2)$]. "Purification" of the major enantiomer X_1 from X_3 will be very efficient if there is a large difference in the value of k_i's. This means that the chiral reagent has strong intrinsic enantiotopic face-differentiating ability as well as a high sensitivity to the stereocontrol of R and R' groups (e.g., syn addition with respect to R in rotamer **A**). These hypotheses involve a combination of effects ["reagent control" combined with "substrate control" (22)]. On these bases, a mathematical model was developed (21) which assumed that each reaction is first-order in substrate and reagent. An analytical solution was found for the case in which there is an excess of reagent (>2 eq.). The ratio of enantiomers is given by eq. [13]:

$$\frac{\mathrm{X}_1}{\mathrm{X}_2} = \left(\frac{\delta_1(\delta_3 + \delta_4)}{\delta_3(\delta_1 + \delta_2)}\right)\left(\frac{a - (\delta_1 + \delta_2) - 1}{a - (\delta_3 + \delta_4) - 1}\right) \qquad [13]$$

In this equation $\delta_i = k_1/\Sigma k_i$ (fractional rate constant) and $a = [\mathbf{D}]/[\mathbf{D}_0]$ (fractional substrate concentration). At low conversion $X_1/X_3 = k_1/k_3$. Equation [13] shows that the ratio of enantiomers can become as large as desired just by achieving a conversion C ($C = 1 - a$) that is large enough. This conclusion is typical for most kinetic resolutions, as already discussed.

Asymmetric epoxidation by the Sharpless reagent was investigated on **A** ($R = \mathrm{OH}$, $R' = \mathrm{H}$). This seems promising because Sharpless epoxidation often gives high enantioface differentiation ($k_{re}/k_{si} > 50$) as well as strong enantiomer differentiation in kinetic resolution ($k_R/k_S > 100$) (12).

The increase in enantiomeric excess with conversion time for epoxy alcohol was experimentally confirmed using an excess of *t*-BuOOH in the presence of the combination Ti(O*i*-Pr)$_4$/(+)-diisopropyl tartrate at −25°C. The e.e.'s of $X_1(R = \mathrm{OH}, R' = \mathrm{H})$ were 84, 93, and 97% after 3, 24, and 140 h, respectively. The diastereomeric excess was also very high and improved with time (92, 99.7, and 99.7%, respectively) (21). The authors studied asymmetric epoxidation of various achiral divinylcarbinols and always obtained significant e.e. enhancement with conversion. This family of prochiral substrates is very interesting as starting material in asymmetric epoxidation for the preparation of epoxy alcohols of high enantiomeric excess which can further be used in total synthesis of natural products (21, 23–25).

2. *Kinetic Resolution Combined with the Creation of an Asymmetric Center*

When a racemate such as 2-methylcyclohexanone reacts with a chiral reducing agent the product is a mixture of diastereomers (Figure 12). If the conversion is total there is no kinetic resolution, but the cis and trans alcohols can be optically active. Horeau and Guetté (26) established that in such a case there is a relationship which correlates the e.e.'s of the two diastereomers and the diastereomeric ratio: the diastereomeric ratio is equal to the inverse ratio of the e.e.'s. This simple relation allows one to calculate one e.e. by knowing the other and the ratio of diastereomers. For partial conversions, this relation does not hold. It was demonstrated by El Baba et al. (27) that a general

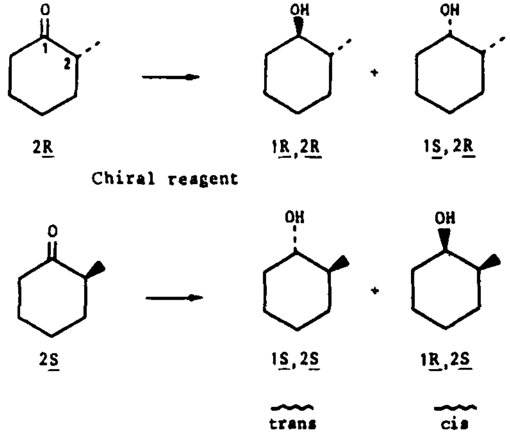


Figure 12. Partial transformation of a racemic mixture with creation of a new asymmetric center (27).

equation links the e.e.'s and the relative amounts of the various species:

$$Y_0 = X_1 Y_1 + X_2 Y_2 + X_3 Y_3 \qquad [14]$$

In eq. [14], Y_i represent the enantiomeric excesses: Y_0 is the e.e. of the starting material ($Y_0 = 0$ if it racemic); Y_1 is the e.e. of the recovered starting material after partial conversion C; Y_2 and Y_3 are e.e.'s of the diastereomeric products; and X_i represents the fractional amount of the chiral species characterized by Y_i values. Equation [14] is based on the material balance involving the chiral species. It was obtained without reference to a hypothetical kinetic scheme. If one starts from a racemate ($Y_0 = 0$), it is possible to express Y_i as a function of the diastereomeric ratio $x = X_2/X_3$ and conversion. It is also possible to give an analytical expression for C or x:

$$Y_1 = f(Y_2, Y_3, x, C), \qquad Y_2 = f(Y_1, Y_3, x, C), \qquad Y_3 = f(Y_1, Y_2, x, C)$$

$$C = f(Y_1, Y_2, Y_3, x), \qquad x = f(Y_1, Y_2, Y_3, C)$$

These relations will not be analyzed in detail here but can be found in ref. 27. They involve sign conventions. These relations may be used to check the self-consistency of a set of data coming from a kinetic resolution (for a discussion, see ref. 27). Another application of these equations is to use the set of most accurate values for computing the least accurate one.

A limiting case is that in which one of the two diastereomeric products is present in too small an amount to be detected. When asymmetric epoxidation of racemic (E)-$C_6H_{11}CH(OH)CH{=}CHMe$ by Sharpless reagent is stopped at 50% conversion, it gives nearly exclusively erythro alcohol with e.e. $\geqslant$95% (27). The threo epoxy alcohol enrichment was not accurately measured by the routine analytical methods. By hypothesizing about the upper limits of e.e.'s of resolved alcohol and of erythro epoxy alcohol, it is possible to find a relation between the diastereomer ratio and e.e. of the undetected threo epoxy alcohol (27). The specific case of asymmetric epoxidation of (E)-$C_6H_{11}CH(OH)CH{=}CHMe$ was carefully studied in the Sharpless group (12) and the various rate constant ratios were measured. The curve of Figure 13 could be drawn till 100% conversion of the racemic mixture. It is informative to visualize the evolution of yields and e.e.'s for the diastereomeric products, even in the slow-reacting stage (after 50% conversion). For another example of efficient kinetic resolution as well as high diastereoselective product formation (in the hydrogenation of racemic β-hydroxyacrylates catalyzed by a chiral rhodium complex), see the report of Brown (28) and Sect. III-A).

The two stereoselectivity factors **s** and **s**′ (concerning reactions on the R and S enantiomers) are invariant with conversion extent and can be expressed as a function of Y_2 or Y_3 (27). In a kinetic resolution performed to various

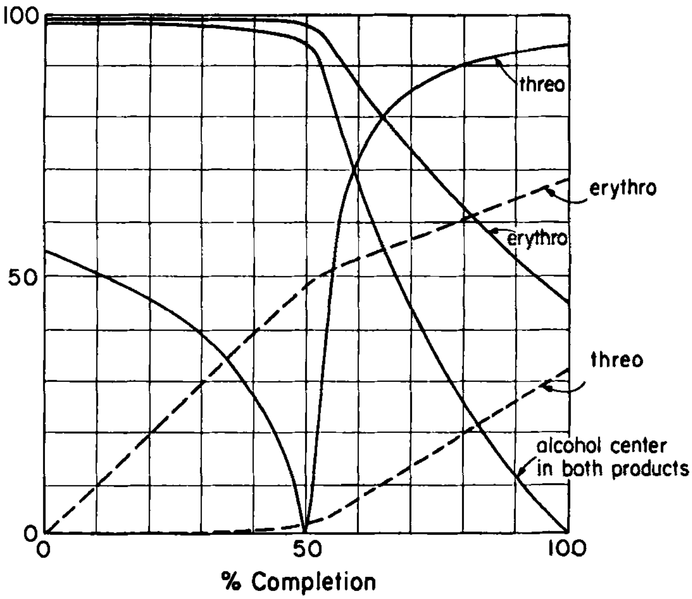


Figure 13. Asymmetric epoxidation of racemic (*E*)-$C_6H_{11}CH(OH)CH{=}CHMe$ (12): --- yields (%) and —— e.e.'s (%) of diastereomeric epoxy alcohols versus conversion. The e.e. of the alcohol center in both products is the e.e. of the allylic alcohol that would be obtained from complete deoxygenation of the diastereomeric epoxy alcohols (K. B. Sharpless, private communication).

extents of conversion *C*, the corresponding **s** and **s**′ factors can be calculated for each conversion and should be constant. If there is a change with *C*, it means that there is an evolution of the structure of the chiral auxiliary (reagent or catalyst) during the course of the reaction. Such a case could be established in the asymmetric hydrogenation of racemic dipeptide NAcΔPheAlaOMe (ΔPhe = dehydrophenylalanine) catalyzed by RhCl(diop) (27).

G. Mutual Kinetic Resolution

Mutual kinetic resolution means that there is a reaction between two partially resolved chiral compounds (*R*, *S* and *R*′, *S*′) with formation of diastereomeric products (*RR*′, *SS*′ and *RS*′, *SR*′):

$$R + R' \xrightarrow{k_{RR'}} RR' \qquad [a]$$

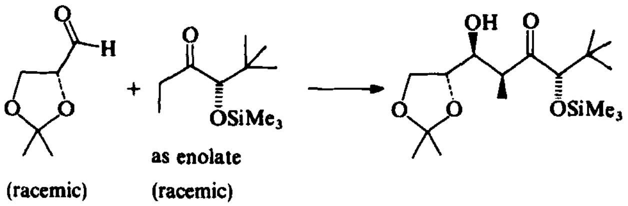
$$S + R' \xrightarrow{k_{SR'}} SR' \qquad [b]$$

$$R + S' \xrightarrow{k_{RS'}} RS' \qquad [c]$$

$$S + S' \xrightarrow{k_{SS'}} SS' \qquad [d]$$

The previous cases of kinetic resolution implied only consideration of eqs. [a] and [b], for example, where R' is the chiral reagent B as in eqs. [1] and [2]. By taking the set of the four reactions [a]–[d], there are no additional stereoselectivity factors since $k_{RR'} = k_{SS'}$ and $k_{RS'} = k_{SR'}$. Hence $\mathbf{s} = k_{RR'}/k_{SR'} = k_{SS'}/k_{RS'} = k_{RR'}/k_{RS'} = k_{SS'}/k_{SR'}$. For a very high **s** factor one can expect preferred formation of one diastereomer, whatever the initial enantiomeric excesses of the two reactants may be. The set [a]–[d] can be treated as a "quadruplet of second order parallel reactions" (18). Ugi et al. pointed out that the corresponding four differential equations cannot be solved explicitly, but only numerically (18). They gave tables and figures concerning enantiomeric excesses of the recovered reactants after various extents of conversion when one starts from equimolar amounts of a racemic reactant and another reactant with 90 or 10% e.e., for stereoselectivity factors ranging between 3 and 300. However far the reaction proceeds, and whatever the magnitude of **s** ($\mathbf{s} > 1$), the enantiomeric excesses of both components of the system *simultaneously* increase, hence the term mutual kinetic resolution. Even a mixture containing racemic R', S' can enrich a slightly resolved R, S mixture to any degree of e.e. if the **s** factor departs from 1, by selecting the proper extent of conversion C. This may be a mechanism responsible for the amplification of optical activity in prebiotic chemistry. Horeau (29) envisaged such a process and performed model experiments involving the esterification of alcohols of small e.e.'s with racemic or partially resolved α-phenylbutyric anhydride or chloride. Horeau (17, 29) also pointed out that the **s** factor in such a system is accurately measured by reaction between racemic reactants. The stereoselectivity factor **s** is equal to the ratio of the diastereomeric products $(RR' + SS')/(SR' + RS')$. This ratio is independent of the extent of conversion and of the initial relative amounts of reactants. This method applies very well to esterification whose **s** factor is easily deduced from the GC analysis of diastereomers. For example, reaction between racemic α-phenylbutyric anhydride and racemic $PhCHOHCH_3$ in pyridine gave an **s** factor of 4.7 (17). Similarly racemic α-phenylbutyric acid chloride and racemic mesityl$CH(OH)CH(Me)_2$ gave a value of $\mathbf{s} = 6.5$ (29). A set of sequential partial esterifications between these two reactants (each with 0.1% e.e.) led finally to the recovery of the same compounds, each with 95% e.e. (29).

An apparently more complex situation has been discussed by Heathcock et al. (30), involving aldol condensation between chiral aldehydes and chiral ketones, with concomitant formation of two asymmetric centers (erythro relative configuration). Only one diastereomer was obtained in the following reaction involving two racemic reactants:



A discussion of such cases can be found in ref. 31. For other examples see also refs. 32–34. Chiral discrimination is very high when an enolate $[(\eta^5\text{-}C_5H_5)Fe^*(CO)(PPh_3)(COCHR)]^-\ Li^+$ ($R = H$ or Me) opens propene oxide or *trans*-2-butene oxide by an S_N2 process in the presence of a Lewis acid. In reactions performed between racemic reactants (iron is an asymmetric center in the complex), selectivity factors up to 30 were observed (35, 36). Pinacol formation from racemic ketones sometimes occurs with good mutual kinetic resolution, as found in reductive dimerization of an α,β-unsaturated ketone (37) or camphor pinacolization (38). In the second case, racemic camphor in the presence of lithium in THF or liquid ammonia gives only the racemic pinacol formed by combination of two camphor units of the same absolute configuration. Interestingly, in THF the pinacol is formed with an endo:endo link, while in NH_3 the exo:endo stereochemistry was obtained.

If the measured stereoselectivity factor **s** is very large during combination between chiral or racemic moieties, it may be possible to synthesize optically active compounds using one of the reactants as a racemic mixture:

$$\underset{\text{excess}}{(R+S)}+R' \longrightarrow RR'$$

Such an example is mentioned in Sect. III-B-11.

An enhancement of the enantiomeric excess of a compound is possible without the help of a chiral reagent or catalyst when the compound is able to react with itself to give a dimer, for example. This situation is schematically shown by eqs. [a]–[d] where $R = R'$ and $S = S'$, and is detailed in Sects. II-J and K.

Coupling of two chiral fragments during the course of a total synthesis of natural product is a standard methodology in modern organic chemistry. Sometimes one or both fragments are derived from the chiral pool or result from an efficient asymmetric synthesis, but nevertheless are not enantiomerically pure (let us assume 90% for both fragments). One product (the desired one) will predominate and its e.e. is expected to be close to 90% also.

This assumption can lead to misleading data, even if there is no mutual kinetic resolution (**s** = 1 in the [a]–[d] set). A statistical distribution in the coupling reactions will afford two diastereomers (in the ratio 9.5:1) with 99.5% e.e. and 0% e.e. for the major and minor one, respectively. These cases have been discussed by Eliel in the synthesis of (−)-malyngolide (39), by Midland in the synthesis of (−)-talaromycin A (40), and by Mori et al. in pheromone synthesis (41). Even in the absence of chiral recognition during the coupling stage, there is a large enantiomeric enrichment for the major product. However far the reaction proceeds, the e.e.'s of the two starting materials remain unchanged. The situation is different if there is some chiral recognition (**s** > 1). There will be a departure from the values calculated for the diastereomer ratio and for various e.e.'s on the basis of statistical reactions. A detailed analysis was performed by Heathcock et al. (30) on coupling reactions via aldol condensation in which two chiral centers are created as a result of addition whose stereochemistry occurs with double asymmetric stereodifferentiation or double asymmetric synthesis (23). The inherent diastereoface selectivity shown by each compound in its reaction with achiral partners roughly correlates with the degree of mutual kinetic resolution.

A simple way to distinguish between statistical coupling and kinetic resolution is suggested here on the following basis: in a statistical coupling there is no change in the e.e.'s of reactants and in the diastereomer product ratio during the whole course of the reaction. Similarly the e.e.'s of the diastereomeric products remain constant.

The specific case of coupling of a chiral reactant with itself (duplication or triplication) is described in Sect. II-J. Asymmetric polymerization (Sect. II-D) is a limiting situation.

The validity of measurements of **s** values using racemic reactants can be invalidated in some cases when the reaction is sensitive to diastereomeric solute–solute interactions of enantiomers in achiral solvents (42, 43). These types of interactions could lead to a different stereochemical outcome, according to e.e.'s of the reactants.

H. Nonreciprocal Kinetic Resolution

A kinetic resolution process is satisfactorily approximated by the pair of parallel equations where *R*, *S* is in excess:

$$R + \mathrm{B}^* \xrightarrow{k_R} \mathrm{P}$$

$$S + \mathrm{B}^* \xrightarrow{k_S} \mathrm{Q}$$

For symmetry reasons one expects that the following pair of parallel reactions will use the same apparent rate constant k_R and k_S ($\bar{\mathrm{B}}^*$ refers to the enantiomer of B*; racemate $\mathrm{B}^*\bar{\mathrm{B}}^*$ is in excess):

$$\mathrm{B}^* + R \xrightarrow{k_R} \mathrm{P}$$

$$\bar{\mathrm{B}}^* + R \xrightarrow{k_S} \mathrm{Q}'$$

Reciprocal kinetic resolution occurs in most cases. This was established in asymmetric esterification, for example (31, 44). The first example of nonreciprocal kinetic resolution was found by King et al. (45, 46). These authors studied kinetic resolution of menthylamine by camphor-10-sulfonyl chloride and vice versa. The stereoselectivity factors were 3 and 1, respectively. Such a discrepancy is related to the formation of an intermediate which modifies the kinetic framework. The intermediate was identified as a sulfene produced from the organic sulfonyl chloride under the influence of the amine. It is interesting to note that 10-camphorsulfonyl chloride is an excellent reagent for the kinetic resolution of an amine, as shown in the course of the total synthesis of delphinine (47).

I. Sequential Kinetic Resolutions

One may expect that the enantiomeric excess of a chiral product coming from a cascade of kinetic resolutions will be enhanced. This seems intuitively obvious, since in the early stages of a kinetic resolution the ratio of enantiomeric products is equal to the selectivity factor $\mathbf{s}_1$ (see Sect. II-A). If these products become the starting material of a new kinetic resolution with a selectivity factor $\mathbf{s}_2$, the ratio of enantiomeric products can be approximated (for a small conversion) to $\mathbf{s}_1 \times \mathbf{s}_2$. With this type of approximation, Yamagata (48) calculated the final ratio of enantiomers as $[R]/[S] = \mathbf{s}_1 \times \mathbf{s}_2 \times \cdots \times \mathbf{s}_n = (\mathbf{s})^n$ if $\mathbf{s}_1 = \mathbf{s}_2 = \cdots = \mathbf{s}_n$ in n consecutive reactions. Even if $\mathbf{s}$ is small ($\mathbf{s} = 1 + \varepsilon$), the final ratio can be as high as desired when n is large enough, since $[R]/[S] = (1 + \varepsilon)^n = \varepsilon n$. This was taken as a potential model for explaining the development of optical activity on Earth.

Recently Sih et al. (49) derived quantitative expressions defining the following kinetic system where two kinetic resolution steps are operating in tandem (P, $\bar{\mathrm{P}}$, Q, $\bar{\mathrm{Q}}$, and R, S are pairs of enantiomers).

$$\mathrm{P} \xrightarrow{k_1} \mathrm{Q} \xrightarrow{k_3} R$$

$$\bar{\mathrm{P}} \xrightarrow{k_2} \bar{\mathrm{Q}} \xrightarrow{k_4} S$$

Here the same chiral catalyst is at work. This situation was studied in the specific case of the microbial enantioselective hydrolysis of racemic 2,2'-diacetoxy-1,1'-binaphthyl where $k_1 > k_2$ and $k_3 > k_4$ (the enzyme retains the same stereochemical preferences). Some pseudo-first-order rate constants are indicated in Figure 14. Following a conversion of 50%, (*S*)-binaphtol was isolated in 36% yield with 90% e.e.

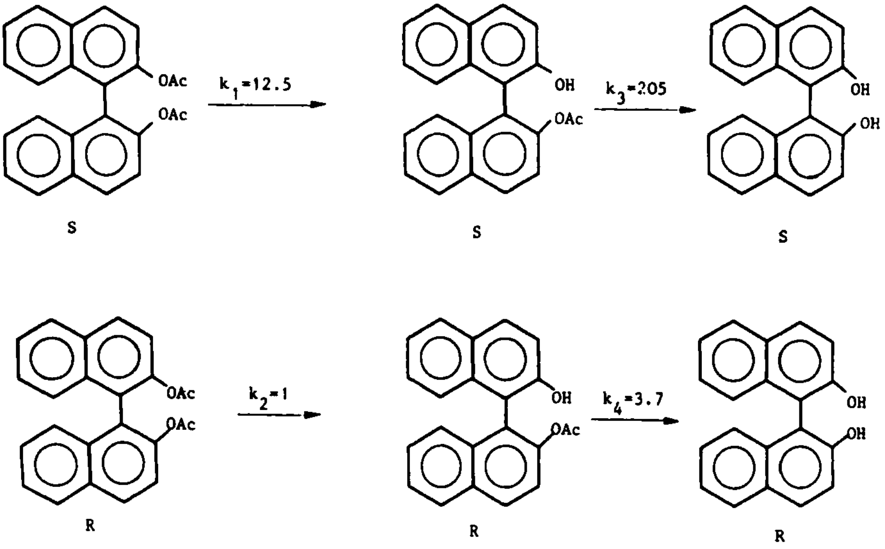


Figure 14. Pseudo-first-order constants in steps occurring during stereospecific hydrolysis catalyzed by *A-glauca* (49).

J. Oligomerization

This section deals with cases in which the chiral substrate (monomer) reacts with itself to form either linear or cyclic dimers, or trimers or oligomers (with the exception of polymers), either directly or through coordination with an organic or organometallic achiral agent (template).

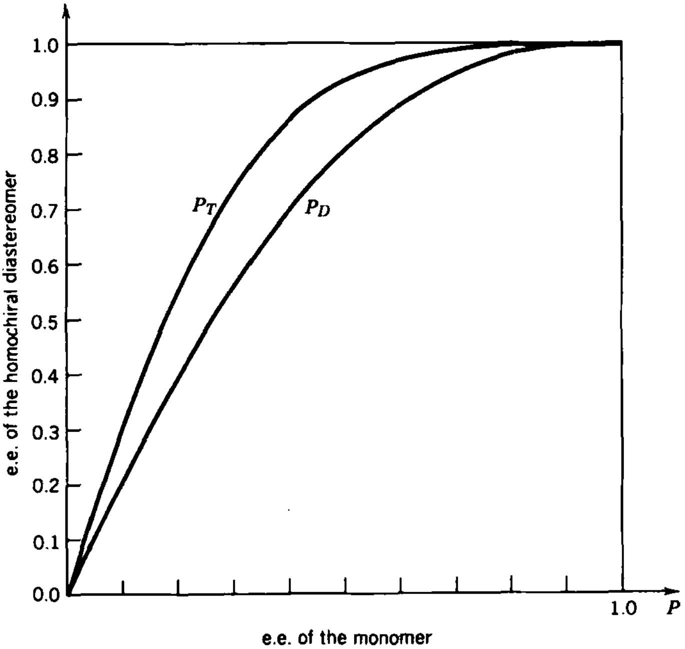
1. Duplication

In the duplication process, an enantiomer reacts with itself or with its enantiomer to give a dimer either directly or via a bifunctional "linking" compound. In the hypothesis where the linking does not bring a new element of chirality, eqs. [a]–[d] of Sect. II-G hold, with $R = R'$ and $S = S'$.

The system is characterized by two different rate constants, $k_e = k_{RR'} = k_{SS'}$ and $k_m = k_{SR'} = k_{S'R}$, which refer to the reaction of enantiomers of the same or different configuration (like or unlike pair of enantiomers) to give, respectively, enantiomeric (homochiral) product e or meso (heterochiral) achiral product m.

The selectivity $\mathbf{s} = k_e/k_m$ can be measured from the racemic substrate as the ratio of the diastereomeric products $e/m = (RR+SS)/(RS+SR)$. From either synthetic or analytical points of view, this dimerization process is valuable only if it operates on a partially resolved substrate. Two applications have been reported for an optically active compound that may undergo such a process: the amplification of its e.e. and the determination of its e.e. without the use of an optically pure auxiliary compound and without the measurement of its optical rotation.

a. Amplification of the e.e. of an Optically Active Substance. The "dimerization" or "duplication" process applied to a partially resolved substrate (monomer) may lead to the amplification of its enantiomeric purity in the



(a)

Figure 15(a)

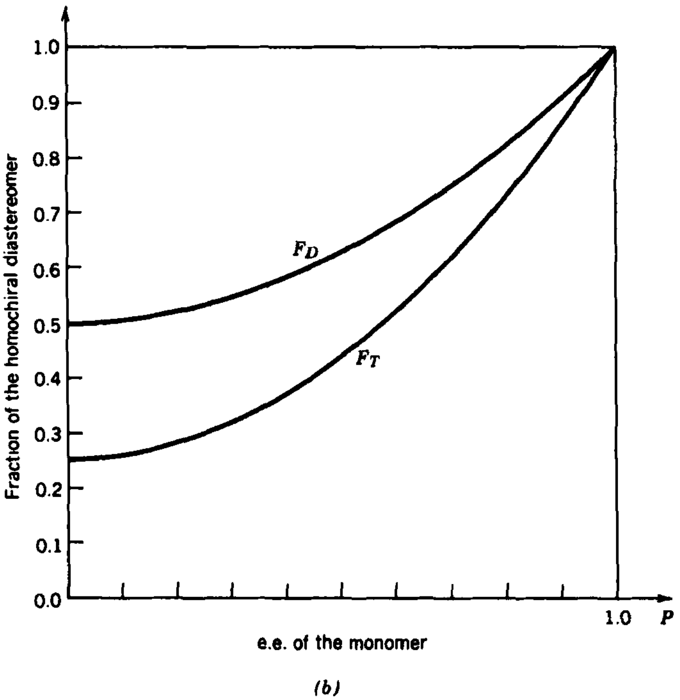


Figure 15. (*a*) Enantiomer excess (P_D, P_T) and (*b*) molar fraction (F_D, F_T) of the homochiral diastereomers versus the e.e. (*p*) of the monomer in duplication (50) or trimerization (51) processes.

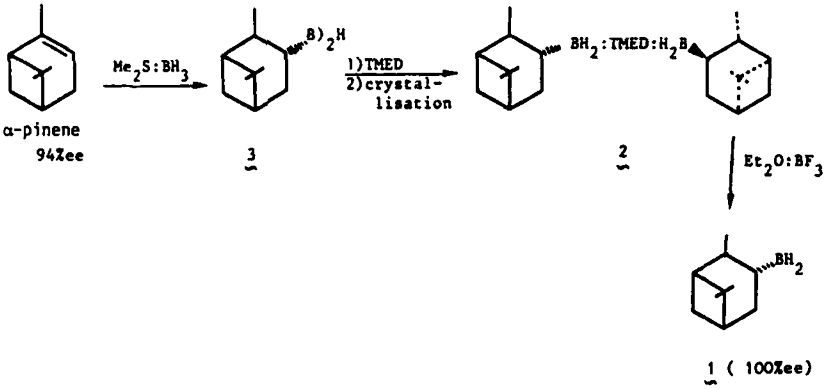
$$P_D = \frac{[RR]-[SS]}{[RR]+[SS]} = \frac{2p}{1+p^2}; \qquad P_T = \frac{[AR_3]-[AS_3]}{[AR_3]+[AS_3]} = \frac{p(3+p^2)}{1+3p^2}$$

$$F_D = \frac{[RR]+[SS]}{\Sigma[\text{dimers}]} = \frac{1}{2}(1+p^2); \qquad F_T = \frac{[AR_3]+[AS_3]}{\Sigma[\text{trimers}]} = \frac{1+3p^2}{4}$$

homochiral dimer, even if no stereoselectivity has been displayed (**s** = 1). In that particular case (**s** = 1), the molar fraction of the homochiral (and hence of the meso) product and its e.e. can be expressed versus the e.e. of the starting material (monomer) (50, 51) (Figure 15).

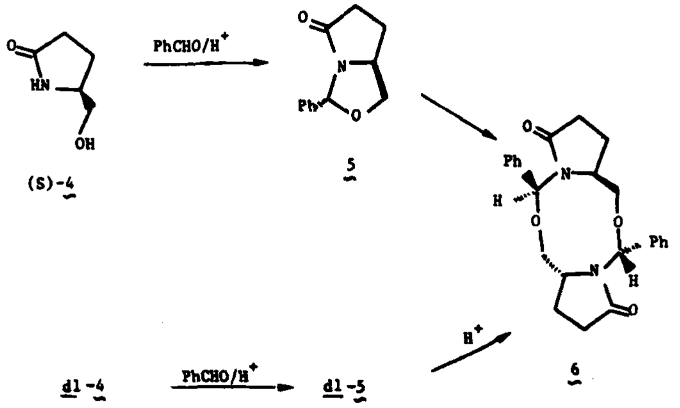
From Figure 15 it can be seen that the e.e. of the homochiral dimer and hence of the constituting monomer is higher than the e.e. of the starting monomer. This is always the case, irrespective of the **s** value. The best situation is the one in which the formation of the meso dimer is favored ($k_m > k_e$). In this case, the minor enantiomer of the monomer would be mainly captured by the meso diastereomer. The worst situation is encountered when the homochiral diastereomer formation is preferred ($k_e > k_m$). In any case, however, provided that the monomer can be recovered from the isolated homochiral dimer, the recovered monomer will exhibit a higher e.e. than that of the starting monomer.

As an example, monoisopinocampheylborane ($IPCBH_2$) **1** could be prepared in an e.e. approaching 100% from α-pinene of ≈94% e.e. via isolation of the bis-tetramethylethylenediamine adduct **2** obtained by reaction of tetramethylethylenediamine (TMED) with IPC_2BH **3** (52). The adduct **2** crystallizes out and shows high e.e.


α-pinene
94%ee
Me2S:BH3
B)2H
3
1)TMED
2)crystal-
lisation
BH2:TMED:H2B
2
Et2O:BF3
BH2
1 (100%ee)

Carrying out a meso-selective reaction (one that reflects the strong preference for the combination of reactants of opposite configuration) could constitute a highly efficient process for the enrichment in one enantiomer of a partially resolved enantiomeric mixture.

Acid-catalyzed condensation of (*S*)-5-(hydroxymethyl)-2-pyrrolidinone-4


O
HN
OH
(S)-4
PhCHO/H+
O
N
Ph
O
5
O
Ph
N
H
O
O
Ph
N
H
O
6
H+
dl-4
PhCHO/H+
dl-5

with benzaldehyde gives only an optically active monomeric oxazoline **5**, whereas racemic **4** gives only the meso compound **6**, through dimerization of racemic **5**. This reaction could be used to increase the e.e. of partially resolved **4** or **5** (53).

b. Determination of the e.e. or the Optical Purity of a Substance. In 1973 Horeau described a general method for determining the e.e. of a substance without measuring its optical rotation and without using an optically active auxiliary compound. The method made it possible for the maximum specific rotation of a chiral compound to be calculated if the optical rotation of a partially resolved sample were known (50).

The method is based on either the "direct" quantitative coupling of enantiomers or analogous quantitative coupling of enantiomers incorporating an achiral reagent. In the absence of any stereoselectivity in the coupling ($\mathbf{s}=1$), a relation can be found between the ratio K of diastereomeric products and the enantiomeric excess p of the starting substance

$$p=\sqrt{\frac{K-1}{K+1}} \qquad [15]$$

Ratio K is generally measured by physical means (e.g., GLC and NMR). An application of the method is the measurement of the e.e. of alcohols through the formation of their carbonates, phthalates, or malonates (50).

In another example, the determination of the e.e. of primary and secondary alcohols, β-hydroxyamides, and esters is based on the conversion of these compounds to phosphonates with PCl_3 as a duplication agent (54). The diastereomeric ratio of the phosphonates is measured by ^{31}P NMR spectroscopy.

The enantiomeric excess of the optically active olefins 1,2-cyclononadiene (55) and *cis,trans*-1,4-cyclooctadiene (56) has been determined from the proportion of diastereomers obtained through dimerization reactions. Such a method has been used (57) for the general case where a mixture of enantiomeric substrates gives diastereomers through coordination with an achiral substance A and when

1. A diastereoselectivity ($\mathbf{s} \neq 1$) is observed in the formation of the achiral meso and the homochiral diastereomers.
2. The diastereoselectivity may be thermodynamic in origin (the diastereomers are formed reversibly).
3. The formation of the diastereomers is not quantitative; an excess of substrate is left free in the solution, whose e.e. (denoted as α) differs from the e.e. of the starting material.

The variable K represents the ratio of diastereomers formed from the chiral substrate of e.e. $=p$ with an achiral reagent, $\mathbf{s}$ is the diastereoselectivity expressed as the ratio of the diastereomers obtained in this reaction with the racemic substrate, and h stands for the relative amount of the uncoordinated substrate.

The values of K, $\mathbf{s}$, and h may be determined through NMR analysis. The enantiomeric ratio R/S in the substrate may be calculated as follows:

$$\frac{R}{S}=\frac{\alpha^3(hK+h+2K+1)+\alpha^2(2K+1)+\alpha(1+hK+h)+1}{\alpha^3+\alpha^2(h+hK+1)+\alpha(2K+1)+2K+1+hK+h}$$

where α stands for the enantiomer ratio (R/S) of the remaining substrate

$$\alpha=\frac{K+\sqrt{K^2-\mathbf{s}^2}}{\mathbf{s}}$$

and the e.e. of the starting material is

$$p=\frac{(R/S-1)}{(R/S+1)}$$

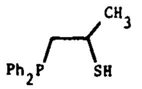
If the amount of remaining starting material is low ($h\approx 0$), the e.e. is given by the simpler equation

$$p\approx\frac{\sqrt{K^2-\mathbf{s}^2}}{K+1} \qquad [16]$$

When $\mathbf{s}=1$, eq. [16] is strictly equivalent to eq. [15].

In principle, this procedure may be applied to any bidentate or unidentate molecule able to coordinate to a metal or it may be applied to a complex

$$(R)\text{-}\mathbf{7} + (S)\text{-}\mathbf{7} \xrightarrow[-2H^+]{Ni^{2+}} (R,R)\text{-}\mathbf{8} + (S,S)\text{-}\mathbf{8} + (R,S)\text{-}\mathbf{8}$$



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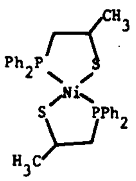

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containing additional, nonlabile ligands. An example of this procedure is the determination of the e.e. of 1-diphenylphosphino-2-propanethiol **7**, through formation of diastereomeric trans nickel complexes **8** (57).

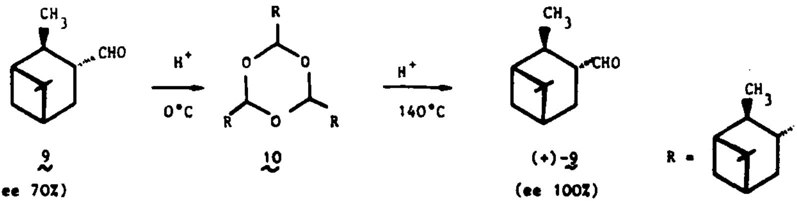
2. *Trimerization, Triplication*

In a trimerization reaction in which an enantiomerically enriched compound reacts with an achiral reagent A, four diastereomers are produced AR_3, AR_2S, ARS_2, and AS_3. Assuming that there is no chiral recognition (i.e., that all the rate constants are equal), a probabilistic approach can be made, and the molar fraction and the e.e. of symmetrical trimers produced on completion of the reaction (AR_3 and AS_3) can be calculated versus the optical purity of the monomer (Figure 15). Examination of these curves indicates that trimerization of enantiomerically unbalanced mixtures of monomers should be considered as a process that is more efficient for the amplification of enantiomeric purity than is dimerization. A satisfactory agreement has been found between experiment and theory in triplication experiments involving the reaction of propylene oxide of various optical purities with ammonia (51).

3. *Cyclooligomerization*

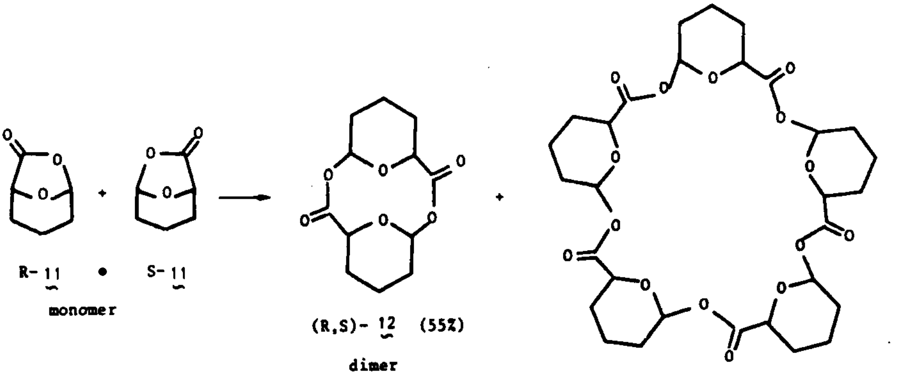
During the linear polymerization of a monomer, when the number, disposition, and constitution of monomers in a chain are adequate, the resultant oligomer may undergo a cyclization, thus limiting the growth of the chain. The optical purity of the dimers, trimers, and so on that contain enantiomer molecules of the same configuration is often higher than the e.e. of the original monomer. If separation of the homochiral oligomers is possible, subsequent depolymerization will afford a monomer with an optical purity higher than that of the starting material.

A simple case in which a cyclic oligomer of specific ring size is predominantly or selectively formed is the trimerization of 3-formylpinane **9**, which was obtained in 70% e.e. from the optically impure commercial α-pinene. Trimerization of **9** in acidic medium gave the tripinyl trioxan **10**, the homo-



chiral diastereomer of which was purified by crystallization. Depolymerization of **10** led back to enantiomerically pure (+)-**9** (58).

One interesting case demonstrates that the ring size for cyclization is under the control of the stereochemical composition of the constituting monomers (59). In a study of the oligomerization of 6,8-dioxabicyclo[3.2.1]octan-7-one (**11**), cyclization stops at the dimer stage in the case of reaction between heterochiral **11** molecules, while the analogous reaction between homochiral **11** molecules leads directly to oligomers; no trimer is detected and macrotetrolides and pentalides are racemic mixtures of homopolymers (constituted of monomer units of the same configuration). Under properly devised conditions, an enantiomerically unbalanced monomer mixture gives rise to the optically active macrotetrolides and macropentalides, together with optically inactive macrodiilide. As an example, oligomerization of **11** (36% e.e.), gives after 4 days reaction 55% racemic diilide **12** and 27% pentalide (98% e.e.) **13** (59).



R-11 • S-11
monomer

(R,S)-12 (55%)
dimer

$(R)_5$-13 + $(S)_5$-13 (27%, 98% ee)
pentamers

K. Polymerization

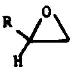
When a racemic mixture of monomers reacts in a polymerization process under the influence of a chiral catalyst, one can expect the enantiomeric purity of the monomer to increase as long as the reaction proceeds. Polymerization differs from oligomerization (see Sect. II-J) only in the number of monomers that are incorporated in the product. Usually this number is very high in polymerization. The general scheme of asymmetric polymerization is quite complicated since the enantiomers of the monomer can be incorporated to various extents in the growing chain (60). A simplified scheme is

$$\underset{(R=S)}{\text{Racemic monomer}} \xrightarrow[\text{catalyst}]{\text{Optically active}} \underset{(R>S)}{\text{Optically active polymer}}$$

$$+ \underset{(S>R)}{\text{Unreacted monomer}}$$

Pino et al. (61, 62) have observed a slight preference for polymerization of one of the enantiomers of a racemic α-olefin such as 3-methyl-1-pentene in a reaction catalyzed by an optically active Ziegler–Natta catalyst [i.e., $TiCl_4 + Zn(CH_2\text{-}C(Me)H\text{-}Et)_2$].

They named this type of reaction *stereoelective polymerization.* It is equivalent to a *kinetic resolution during a polymerization.* We will not discuss here the various structures of the polymers that may be formed in such polymerizations. For more details see refs. 61–63. One of the most thoroughly studied kinetic resolutions associated with a stereoelective polymerization concerns strained heterocycles such as **14**–**17**.



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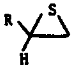

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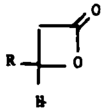

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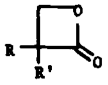

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The main results were reviewed in refs. 63 and 64. Anionic opening of the rings initiated by various organometallic alkoxides leads to polymers such as polypropylene oxide (monomer **14**, R = Me). The catalysts generally contain a divalent metal (zinc or cadmium). Optically active catalysts were easily prepared by mixing, for example, diethylzinc and a chiral alcohol R*OH (or a diol). Depending on the structure of the alcohol, the initiator may consist of associated species such as $(EtZnOR^*)_x$ or $(R^*OZnOR^*)_y$ of varying composition. General rules were given to correlate the absolute configuration of the chiral auxiliary with the absolute configuration of the fast-reacting monomer (64). It seems that the active sites for polymerization also involve coordinated molecules of solvent or monomer. Measurements established that the stereoselectivity factor **s** is constant during the course of the reaction. However, according to the nature of the initiator system, three kinetic laws apply to stereoelective polymerization. The most frequently applicable is a first-order law with respect to each enantiomer; a less common case is a second-order law. Most of the authors (63, 64) working in the area of kinetic resolution by asymmetric polymerization use eq. [17] to find the selectivity factor **s**:

$$(1-C)^{\mathbf{s}-1}=\frac{1+\text{e.e.}}{(1-\text{e.e.})^{\mathbf{s}}} \qquad [17]$$

In this equation, e.e. refers to the enantiomeric excess of remaining monomer and C to conversion. It is easy to demonstrate that eq. [17] is strictly equivalent to eq. [4].

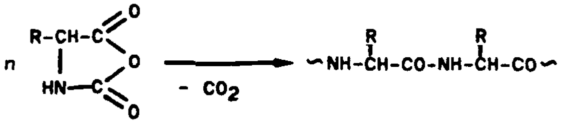
It is important to notice that the **s** factor is sometimes modified by the initial enantiomeric composition of the monomer. With thiiranes there is a linear correlation between the value of **s** and the initial e.e. of thiiranes. Here, it appears that the chiral initiator gives an irreversible complexation or reaction with the monomer. The active site is then produced and does not change during the polymerization. If one takes methylthiirane as monomer (**15**, R = Me), and $ZnEt_2$-(*R*)-3,3-dimethyl-1,2-butanediol as catalyst precursor, the **s** factors are 2.3, 4.4, and 8.0 for thiirane of e.e. = 0, 35, and 55%, respectively. Such a large increase in **s** made it possible to prepare methylthiirane with 98% e.e. starting from the racemic mixture. After 50% conversion had been achieved, the thiirane was reisolated and polymerized again to 50% conversion. Repetition of this process led to an e.e. of 98%.

It is impossible to present in detail the various facets of kinetic resolution of these small heterocycles which can be of preparative value. For more details, see refs. 63 and 64.

It is remarkable that the $ZnEt_2$-(*S*)-2,2′-dihydro-1,1′-binaphthyl gave a **s** factor close to 20 in kinetic resolution associated with the polymerization of racemic methylthiirane (50).

Polymerization of α-amino acid *N*-carboxylic acid anhydrides (**18**) has been widely investigated and has been reviewed (63); only a few points are reported here.

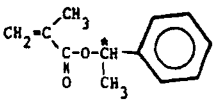
Polymerization of **18** can be initiated by various achiral or chiral additives. Careful experiments established the influence of the initiator as well as the effect of the growing chain, especially when the chain takes on an α-helix conformation on the polymer structure. Numerous experiments support the idea that it is the helicity and/or the configuration of the terminal residues close to the reactive center that determine the stereoselectivity of monomer



18

incorporation in the growing chain. The distribution of amino acid moieties in the polymers was also studied in great detail. The polymerization of polypeptides prone to give regions of β-sheet conformation was also investigated (66). Analysis of the β-sheet domains shows an almost perfect homochiral composition (66). Polymerization of racemic α-amino acids with a chiral initiator or partially resolved α-amino acids with an achiral catalyst has been widely discussed as a potential model for the creation and amplification of optical activity in prebiotic times. Enantiomer enrichment in the prebiotic peptides combined with kinetic resolution of almost racemic monomers could occur as a result of α-helix control [a concept originally proposed by Wald (67)] or to β-sheet control (63, 66).

Very efficient kinetic resolution of α-methylbenzyl methacrylate (**19**) was recently described by Okamoto et al. (68). A variety of chiral catalysts was easily obtained by combination of Grignard reagent (RMgX) and sparteine



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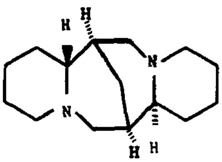


20

(**20**) or its derivatives. The reaction was carried out in toluene at −78 °C. The most stereoselective catalyst appeared to be the complex formed between cyclohexylmagnesium bromide and sparteine: when $C = 51.8\%$ the e.e. of recovered **19** was 83%, which translates to an apparent selectivity factor of 20 by application of eq. [4]. The process was treated as a copolymerization of *R* or *S* monomers (C* = metal to which sparteine coordinates):

$$\sim S-C^*+S \xrightarrow{K_{SS}} \sim S-C^*S \xrightarrow{k_{SS}} \sim S-C^*$$

$$\sim S-C^*+R \xrightarrow{K_{SR}} \sim S-C^*R \xrightarrow{k_{SR}} \sim R-C^*$$

$$\sim R-C^*+S \xrightarrow{K_{RS}} \sim S-C^*R \xrightarrow{k_{RS}} \sim R-C^*$$

$$\sim R-C^*+R \xrightarrow{K_{RR}} \sim R-C^*R \xrightarrow{k_{RR}} \sim R-C^*$$

The stereoselectivity factors $\mathbf{s}_S$ $(k_{SS}K_{SS}/k_{SR}K_{SR})$ and $\mathbf{s}_R$ $(=k_{RR}K_{RR}/k_{RS}K_{RS})$ have been estimated to be 33.7 and 0.27, respectively. It appears that the efficiency of enantiomer selection in favor of the *S* monomer depends on the chiral auxiliary (C*) and also on the configuration of the asymmetric center of the last residue of the growing end. X-Ray analysis of various complexes permitted a schematic structure of the active center to be proposed.

III. PREPARATIVE CHEMISTRY

Racemic substrates are usually resolved by the formation of covalent or ionic diastereomeric compounds with an optically pure auxiliary compound. The two diastereomers are then separated and cleaved to afford the two enantiomers of the substrate. This route is fruitful when the compound to be resolved has an acidic or basic character. For compounds without functionality or a group able to readily form a diastereomeric derivative with optically active auxiliary compounds, kinetic resolution may be a valuable alternative. This is true for olefins, alkyl halides and ketones.

This section is divided into two parts, according to the nature of the chiral auxiliary compound (organic, organometallic, or enzymic) and the way in which it is involved (catalytically or stoichiometrically) in the kinetic resolution.

A. Catalytic Methods

1. Enzymatic Reactions

Enzymatic procedures have long been used for the production of optically active compounds from racemic material. Among the six main groups of enzymes (69), hydrolases and oxido-reductases have been by far the most frequently used in kinetic resolution. Enzymatic processes involve either isolated enzymes (with or without the use of coenzymes) or fermentation techniques, carried out with intact microorganisms as a growing culture or resting or liophilized cells. Both enzymes or microorganisms can be used in an immobilized form (70).

In view of the vast number of enzymatic reactions described in the literature, we have restricted this section to those biochemical transformations that are most accessible to chemists—those using commercially available enzymes and yeasts. However some illustrative transformations carried out with readily available microorganisms are included, which either represent a type of reaction or produce a class of important compounds. For the preparation of optically active compounds from racemic substrates mediated by enzymes, we refer the reader to reviews such as refs. 71–74.

The use of enzymes as catalysts for the kinetic resolution of racemic organic substances is of interest for many reasons. Enzymatic systems can catalyze a great variety of organic reactions with high efficiency (up to 10^{12} rate enhancement). They operate under mild conditions (near room temperature and near neutral pH) so that the integrity of other functional groups of the substrate is preserved. Whereas enzymes usually work in aqueous systems, some of them (e.g., lipases) operate best at water–organic interfaces. Thus the latter do not require water-soluble substrates (75).

The key principle underlying all enzyme-mediated kinetic resolutions is that enzymes are able to discriminate between the enantiomers of substrates (enantiomer–substrate selectivity). For enzymatic systems with enantioselectivity **E** < 1, the partially resolved substrate may be recovered and submitted to a second kinetic resolution. The desired optically active compound could then be obtained (through repetitive resolution) with a high enantiomeric excess. However, this would be at the expense of the chemical yield (see Sects. II-E and I). Moreover, such a repetitive procedure could be a way of circumventing a possible inhibition of the catalyst by the product (72).

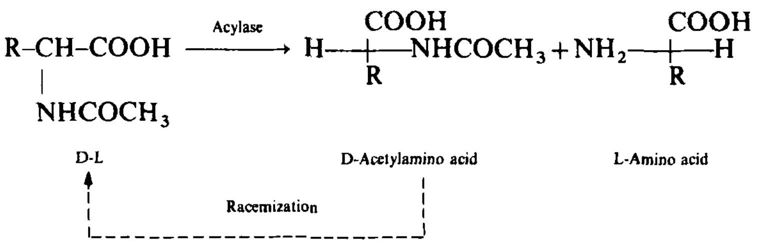
The reactions described below are listed according to the class of enzyme employed (hydrolase, oxido-reductase) and according to the nature of the chemical transformation carried out.

a. Enzymatic Reactions with Hydrolases. The first transformations to be examined are hydrolysis of racemic esters and amides.

$$R\text{-}CONHR' + H_2O \rightarrow RCOOH + R'NH_2 \qquad [18]$$

$$R\text{-}COOR' + H_2O \rightarrow RCOOH + R'OH \qquad [19]$$

Enantioselective hydrolysis of amides has been performed with acylases (EC 3.5.1.n) as catalysts. The most widely used acylases for these preparative resolutions are renal acylases from hog kidney. Acylase I (EC 3.5.1.14) stereoselectively hydrolyzes the L-enantiomers of a broad range of amino acid derivatives according to eq. [20]:

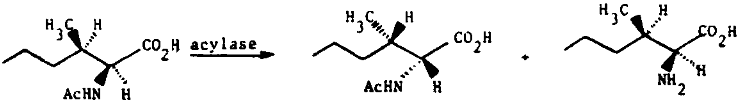


$$\underset{\text{D-L}}{\underset{\displaystyle NHCOCH_3}{\underset{|}{R\text{-}CH\text{-}COOH}}} \xrightarrow{\text{Acylase}} \underset{\text{D-Acetylamino acid}}{H\text{—}\overset{COOH}{\underset{R}{+}}\text{—}NHCOCH_3} + \underset{\text{L-Amino acid}}{NH_2\text{—}\overset{COOH}{\underset{R}{+}}\text{—}H} \qquad [20]$$

After separation from the L-amino acid product, the unreacted *N*-acyl-D-amino acid can be recycled via acid-catalyzed racemization.

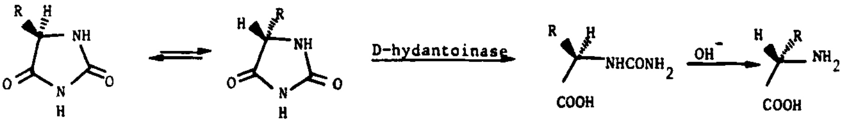
Acylase-catalyzed biotransformations are industrially important for the production of optically active amino acids (76). As an example, L-phenylalanine, the important building block for the low-calorie sweetener aspartame, is produced on an industrial scale by enzymatic resolution of *N*-acetyl-DL-phenylalanine in a continuous process catalyzed by acylase immobilized on DEAE-Sephadex (77). Routes to carnitin and propanolol have been described that involve selective hydrolysis of *N*-phenacetyl derivatives of racemic primary amine bearing a *β*-hydroxyl group in processes catalyzed by immobilized benzylpenicillin acylase from *Coli* (78).

Unnatural substrates have also been prepared: (2*R*, 3*S*)-(−)-2-amino-3-methylhexanoic acid (**21**) was obtained enantiomerically pure from the *N*-acetyl derivative of racemic **22**. Two consecutive kinetic resolutions catalyzed by a microbial acylase from *Aspergillus* gave enriched (2*R*, 3*S*)-**22**, which was recrystallized several times to afford, after hydrolysis, enantiomerically pure (2*R*, 3*S*)-**21**, further used for a pheromone synthesis (79).



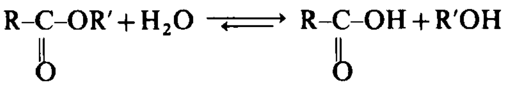
dl -22 (2R,3S)- 22 (2S,3R)-21

Another type of acylase useful in the preparation of *α*-amino acids is hydantoinase (80, 81). Racemic hydantoins (**23**) bearing a variety of *R* groups are readily prepared from aldehydes via the Bucherer reaction. A D-hydantoinase specifically converts D-hydantoins to D-carbamates (**24**). The latter are easily transformed into the corresponding D-amino acid. The unhydrolyzed L-hydantoins can be chemically, or preferably enzymically, racemized. In the latter case, a racemase should be incorporated in the reaction mixture so that the racemization takes place *in situ* as the hydrolysis proceeds (82). D-Phenylglycine and D-(*p*-hydroxyphenyl)glycine (83), which are used in the syntheses of semisynthetic ampicillin, cefalexin, and amoxycillin, are produced by such enzymatic processes.



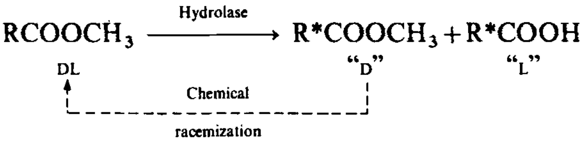
L-23 D-23 24

Another class of reactions promoted by enzymatic systems is the hydrolysis of esters:



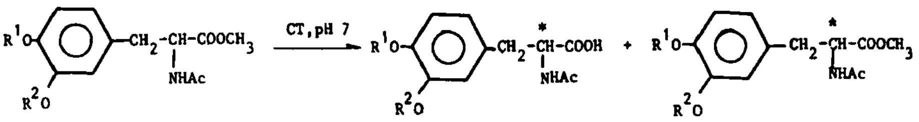
$$R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OR' + H_2O \rightleftharpoons R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OH + R'OH \qquad [21]$$

The chiral moiety of the racemic ester could be in either the acid or the alcohol part of the ester. The preparation of optically active acids has been carried out via enzymic kinetic resolution of the racemic esters prepared with low-molecular-weight alcohols (e.g., methyl, ethyl, and propyl). In eq. [21] the unreacted ester enantiomer can often be recycled via chemical racemization.



$$\underset{DL}{RCOOCH_3} \xrightarrow{\text{Hydrolase}} \underset{\text{“D”}}{R^*COOCH_3} + \underset{\text{“L”}}{R^*COOH} \qquad [22]$$

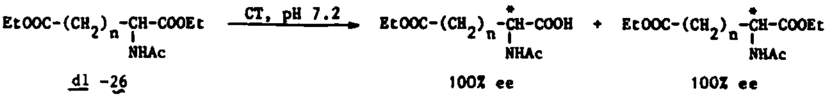
Esters of amino acids have been stereoselectively hydrolyzed with serine proteases such as α-chymotrypsin (EC 3.4.21.1), trypsin (EC 3.4.21.4), or subtilisin (EC 3.4.21.14). All these enzymatic systems exhibit L-stereospecificity and usually applicability to a broad range of substrates (71, 73). Among the numerous α-amino acids and amino acid derivatives resolved with chymotrypsin (CT), we will outline the preparation of L-DOPA (84). Hydrogen bromide-catalyzed hydrolysis of the chymotrypsin–hydrolysis products of **25** affords D- and L-DOPA, which are virtually optically pure. The hydrolyses of racemic aspartic and glutamic ethyl ester (**26**) are stereo-



DL-**25**

$R^1 = H;\ R^2 = CH_3$

$R^1, R^2 = -CH_2-$



dl-**26**

n = 1, 2.

selective (85). Further examples of CT-catalyzed hydrolysis of esters may be found in ref. 65. Chymotrypsin may be used with a broad range of racemic esters of chiral acids, especially bi- and tricyclic ones (Figure 16) (71, 73). Prediction of the stereoselectivity of CT-catalyzed hydrolysis is based on a simple model (86).

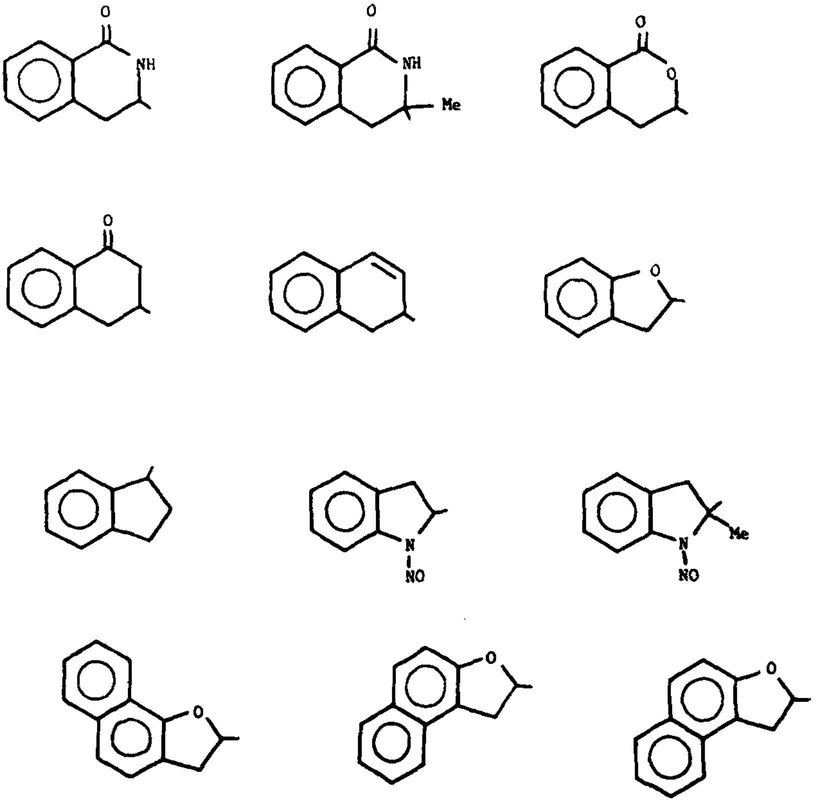
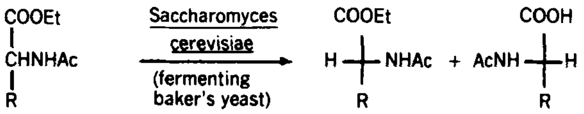


Figure 16. Bi- and tricyclic R in $RCOOCH_3$ resolved by chymotrypsin (71).

The asymmetric hydrolysis of esters of racemic 2,2′-dihydroxy-1,1′-binaphthol with microorganisms affords the optically active binaphtol in up to 97% e.e. at 50% hydrolysis conversion (87). The slow-reacting ester could be recovered with an enantiomeric purity of 94%.

The stereoselective hydrolytic properties of fermenting baker's yeast toward esters of *N*-acetylamino acids (**27**) have been reported (88) (Table 4).

A new enzymatic process for the laboratory-scale preparation of amino acids involves the alkaline catalase-catalyzed hydrolysis of amino acid esters



DL-**27** D-**27** L

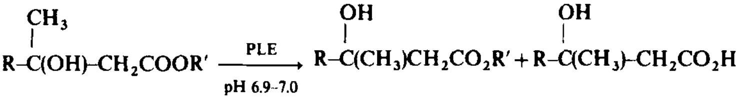
Table 4
Data for Unreacted D-Enantiomer Recovered from Hydrolysis of RCH(NHAc)COOEt Using Fermenting Baker's Yeast[a]

R	Me	Et	*i*-Bu	$PhCH_2$	$(CH_2)_2CO_2Et$
e.e. (%)	100	96	92	97	89
Recovery (%)	47	48	38	38	46

[a] From ref. 88.

(89). Resolution of phenylalanine was carried out on a 25-g scale from its methyl ester by this method.

The use of pig (porcine) liver esterase (PLE) (EC 3.1.1.1.), is increasing in the kinetic resolution of esters, PLE has shown stereoselectivity in the hydrolysis of racemic 3-hydroxy-3-methylalkanoic esters (**28**) (90). The reactions were carried out on a 10-mmol scale, and the e.e.'s of the hydrolyzed and unhydrolyzed substrates were found to be dependent on the conversion of the substrate and on the nature of both R and R′ (Table 5).



$$R\text{–}\overset{CH_3}{C}(OH)\text{–}CH_2COOR' \xrightarrow[\text{pH 6.9–7.0}]{\text{PLE}} R\text{–}\overset{OH}{C}(CH_3)CH_2CO_2R' + R\text{–}\overset{OH}{C}(CH_3)\text{–}CH_2CO_2H$$

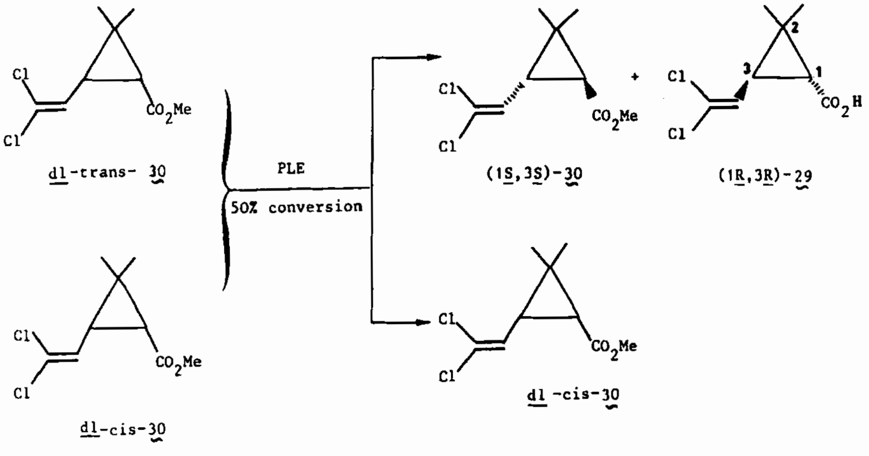
(±)-**28** (*S*)-**28** (*R*)

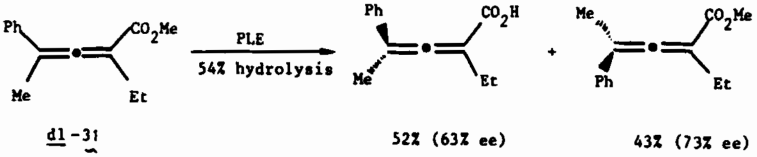
The 1*R*-enantiomers of chrysanthemic and permethrinic acids, used as precursors for pyrethroid insecticides, are interesting targets in organic synthesis (91). They can be prepared on a practical scale (0.2 mol) by PLE-catalyzed enantioselective hydrolysis of their methyl esters. (+)-(1*R*, 3*R*)-Permethrinic acid (**29**) was isolated with an e.e. of 80% through both enantio- and diastereoselective hydrolysis of a mixture of racemic *cis*- and *trans*-methyl esters (**30**) (91). The enantiomeric purity of **29** could be raised to 96% (with 65% recovery) by several crystallizations from petroleum ether. The PLE-catalyzed hydrolysis of racemic allenic esters proceeds with high enantioselectivity. The resolution of **31** is an example (92).

Table 5
Hydrolysis of **28** by Pig Liver Esterase[a]

R	R′	Fraction Hydrolyzed	Recovered Ester(%)	e.e. (%)
CH_3–CH_2	CH_3	0.88	12	98
$(CH_3O)_2CHCH_2$	CH_3	0.67	26	94
$(CH_3O)_2CHCH_2$	CH_3–CH_2	0.75	22	94
CH_2=CH–CH_2	CH_3	0.84	11	94
CH_2=CH–CH_2	CH_3–CH_2	0.50	51	50

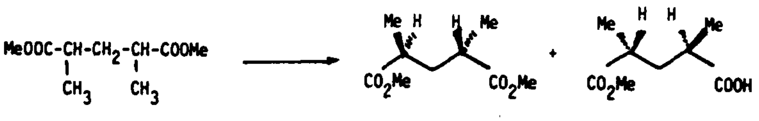
[a] From ref. 90


Cl
Cl
CO2Me
dl-trans-30
Cl
Cl
CO2Me
dl-cis-30
PLE
50% conversion
Cl
Cl
CO2Me
(1S,3S)-30
+
Cl
Cl
2
3
1
CO2H
(1R,3R)-29
Cl
Cl
CO2Me
dl-cis-30


Ph
Me
CO2Me
Et
dl-31
PLE
54% hydrolysis
Ph
Me
CO2H
Et
52% (63% ee)
+
Me
Ph
CO2Me
Et
43% (73% ee)

(*S*)-2-(6-Methoxy-2-naphthyl)propionic acid (naproxen) has been prepared via enantioselective hydrolysis of its 2-chloroethyl ester. The catalyst was the lipase of *candida cylindracea* (93).

A useful chiral synthon for macrolide and polyether antibiotics is the dimethyl (2*R*, 4*R*)-2,4-dimethylglutarate (**32**) (94). This compound was advantageously prepared by microbial esterase-catalyzed hydrolysis of the racemic substrate **33**. In this particular case, however, the unhydrolyzed ester



dl- 33 (2S,4S)- 32 (2R,4R)

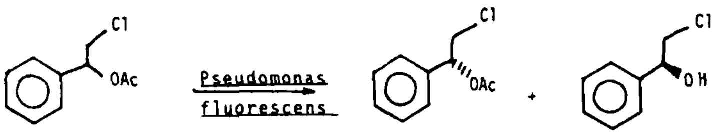
cannot be recyclized because, besides **33**, the nonchiral *meso*-diester diastereomer is produced as a result of epimerization.

Kinetic resolutions of racemic esters in which the alcohol moiety is chiral have also been described. For totally enantioselective transformations, one could have access to both enantiomers of the chiral alcohol, that is, one as the hydrolyzed product, the other being obtained after chemical hydrolysis of the unreacted ester.

A number of 1-arylalkanols of type **34** have been partially resolved via a microbial-catalyzed (*Rhizopus nigricans*) hydrolysis of their acetate (**35**). The process could also be applied to pyridyl carbinols. As an example, 4-pyridyl methyl carbinol could be isolated optically pure through hydrolysis of the acetate of the racemic material (95).

$$\underset{(\pm)\text{-}\mathbf{35}}{\mathrm{ArCH(OAc)CH_3}} \rightarrow \mathrm{Ar\overset{*}{C}H(OAc)CH_3} + \underset{\mathbf{34}}{\mathrm{Ar\overset{*}{C}H(OH)CH_3}}$$

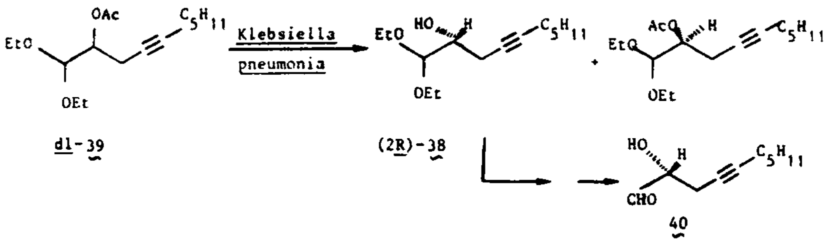
The strategy of the choice of the enzymatic system to be used in a kinetic resolution is illustrated in the asymmetric hydrolysis of (*dl*)-acyloxy-2-chloro-1-phenylethanes (**36**). Among 25 commercially available enzymes, lipase from *Pseudomonas fluorescens* was selected. With this enzyme, hydrolysis of *dl*-**36** proceeded enantioselectively to give (*S*)-2-chloro-1-phenylethanol (**37**) and residual (*R*)-**36** substrate in 100% e.e. (96).



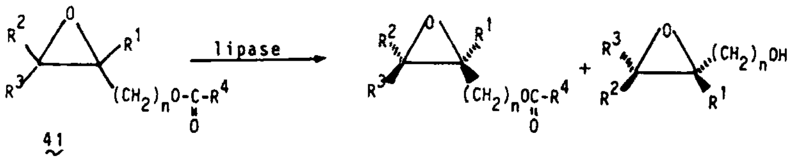
dl- 36 (20%) (R)-36 (100% ee) (29%) (S)-37 (100% ee)

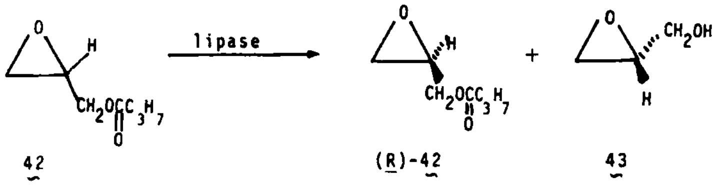
Acetylenic alcohol (2*R*)-**38** was prepared from **39** in 25% yield and 98% e.e. by selective hydrolysis by a microbial esterase (97). (2*R*)-**38** was transformed to the chiron **40**, which was applied to the synthesis of leukotriene B_4.

Whitesides et al. (98) discovered that lipase from porcine pancreas (EC 3.1.1.3), one of the cheapest available enzymes, is able to catalyze the

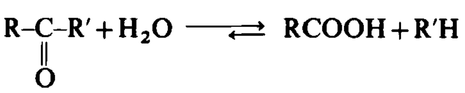

OAc
C5H11
EtO
OEt
Klebsiella
pneumonia
HO
H
AcO
CHO
dl-39
(2R)-38
40

enantioselective hydrolysis of esters **41** of epoxy alcohols, thus providing an interesting alternative to the Sharpless route (12) to useful chiral epoxides. The enzyme is active at water–organic interfaces, does not require water-soluble organic substrates, and works at near neutral pH (7.8) and at room temperature (20°C). The e.e. of the recovered ester was shown to be dependent on the structure of R^4 in **41**. Better results were obtained for long R^4 groups. When a 60% conversion was achieved in the hydrolysis of 300 g of racemic glycidyl butyrate (**42**), 107 g (89%) of (*R*)-**42** with an e.e. of 92% could be recovered. Even though the unreactive epoxy ester cannot be recycled, the high activity, high selectivity, and low cost of this enzymatic system and of the starting material make this a process of high interest for the preparation of chiral epoxy alcohols.


R2
R1
R3
O
(CH2)nO-C-R4
O
lipase
(CH2)nOC-R4
(CH2)nOH
41


O
H
CH2OCC3H7
O
lipase
CH2OH
42
(R)-42
43

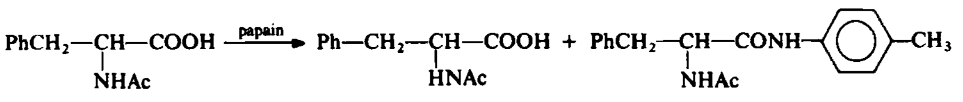
Although the thermodynamic equilibrium in the hydrolysis of esters and amides lies far to the right (eq. [23]), kinetic resolutions of racemic acids or alcohols by the reverse reaction have been achieved.



$$R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R' + H_2O \rightleftarrows RCOOH + R'H \qquad [23]$$

$R' = NHR''$
$R' = OR''$

The reaction must be driven to the left by removal of the product from the aqueous reaction mixture at equilibrium, either through precipitation or extraction with an organic solvent. Amides or hydrazides of amino acids are frequently insoluble in an aqueous reaction medium and thus precipitate as soon as they are formed. Kinetic resolution of *N*-acetylphenylalanine (**44**) by papain-catalyzed amide bond formation was made possible through the choice of a suitable amine (*p*-toluidine), giving rise to an insoluble amide (99).

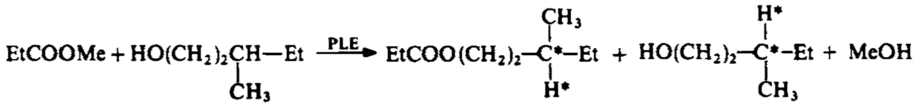


insoluble

(±)-**44** D-**44** L-**45**

A number of *cis*- and *trans*-2-substituted cyclohexanols have been resolved on a practical scale (0.25 mole) through enantioselective "lipase My"-catalyzed ester formation. The lipase, selected from the yeast *Candida cylindracea*, is available in large quantities and catalyzes the synthesis of esters from alcohols and fatty acids in apolar organic solvents (hexane or heptane) at 40°C (100).

Enantiospecific transesterifications catalyzed by immobilized forms of PLE and yeast lipase allow the resolution of a broad range of racemic chiral alcohols (101), an example of which is given in eq. [24].

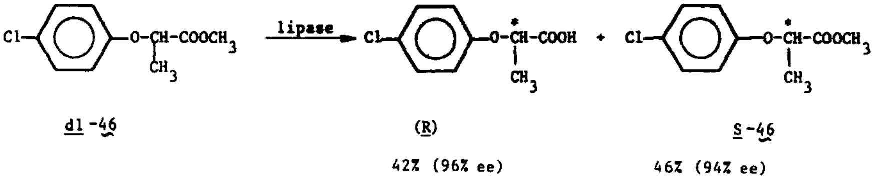


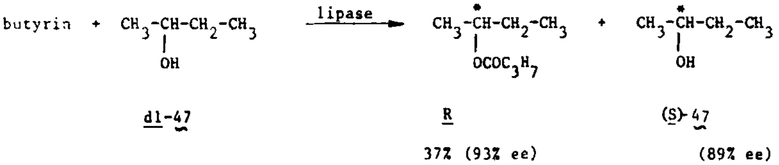
$$\mathrm{EtCOOMe} + \mathrm{HO(CH_2)_2}\underset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{-Et} \xrightarrow{\mathrm{PLE}} \mathrm{EtCOO(CH_2)_2}\!-\!\overset{\mathrm{CH_3}}{\underset{\mathrm{H^*}}{\mathrm{C^*}}}\!-\mathrm{Et} + \mathrm{HO(CH_2)_2}\!-\!\overset{\mathrm{H^*}}{\underset{\mathrm{CH_3}}{\mathrm{C^*}}}\!-\mathrm{Et} + \mathrm{MeOH}$$

(±) (S)

[24]

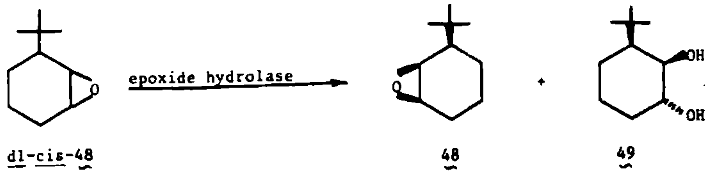
Klibanov has carried out the comparison of three alternative approaches to lipase-catalyzed resolutions of (*R*, *S*)-2-(*p*-chlorophenoxy)propionic acid (**46**) and (*R*, *S*)-2-butanol (**47**): asymmetric hydrolysis, esterification, and a transesterification (102). From the standpoints of productivity, ease of product separation, and the number of steps required, lipase-catalyzed asymmetric hydrolysis has been reported to be superior for the practical resolution of racemic acids, and lipase-catalyzed asymmetric transesterification to be the method of choice for the practical resolution of racemic alcohols. The use of commercially available *Candida cyclindracea* lipase (EC 3.1.1.3.) is of great

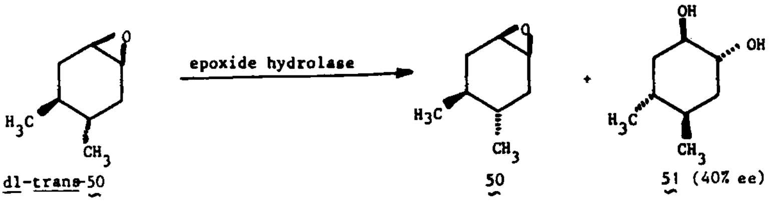

lipase
dl-46
(R)
42% (96% ee)
S-46
46% (94% ee)


butyrin
lipase
dl-47
R
37% (93% ee)
(S)-47
(89% ee)

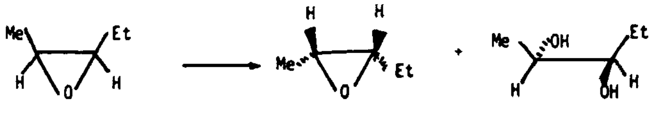
practical value for preparative resolution of racemic acids and alcohols: preparation of optically active compounds on a scale of 100 g can be carried out from 1 L of reaction mixture in the abovementioned resolution.

The enzymatic (rabbit liver microsomal epoxide hydrolase) hydrolysis of racemic *cis*-3-*tert*-butyl-1,2-epoxycyclohexane (**48**) gave (50% conversion) the (1*R*,2*R*,3*S*)-diol **49** with 96% e.e. through exclusive attack at the C-1 position (103). With the same biological medium, racemic *trans*-4,5-dimethyl-1,2-epoxycyclohexane (**50**) was hydrolyzed with moderate enantioselectivity, (−)-epoxide being attacked preferentially to give the (−)-diol **51** (104).


epoxide hydrolase
dl-cis-48
48
49


epoxide hydrolase
dl-trans-50
50
51 (40% ee)

A complete substrate regioselectivity and substrate enantioselectivity was found in the epoxide–hydrolase catalyzed ring opening of racemic *cis*-2-ethyl-3-methyloxirane to give 2,3-pentanediol (105). The (2*R*,3*S*)-oxirane **52** was transformed into the (2*R*,3*R*)-2,3-pentanediol **53**, through regio-



cis-dl-52 53

selective ring opening with Walden inversion at C-3. Other oxiranes (e.g., methyloxirane, ethyloxirane, and epichlorhydrin) also show substrate selectivity toward biotransformations with microsomal rat liver enzymes.

b. Enzymatic Reactions with Oxidoreductases. Alcohol dehydrogenases catalyze oxidoreductions as depicted in eq. [25]:

$$>C{=}O + NADH + H^+ \rightarrow >CHOH + NAD^+ \qquad [25]$$

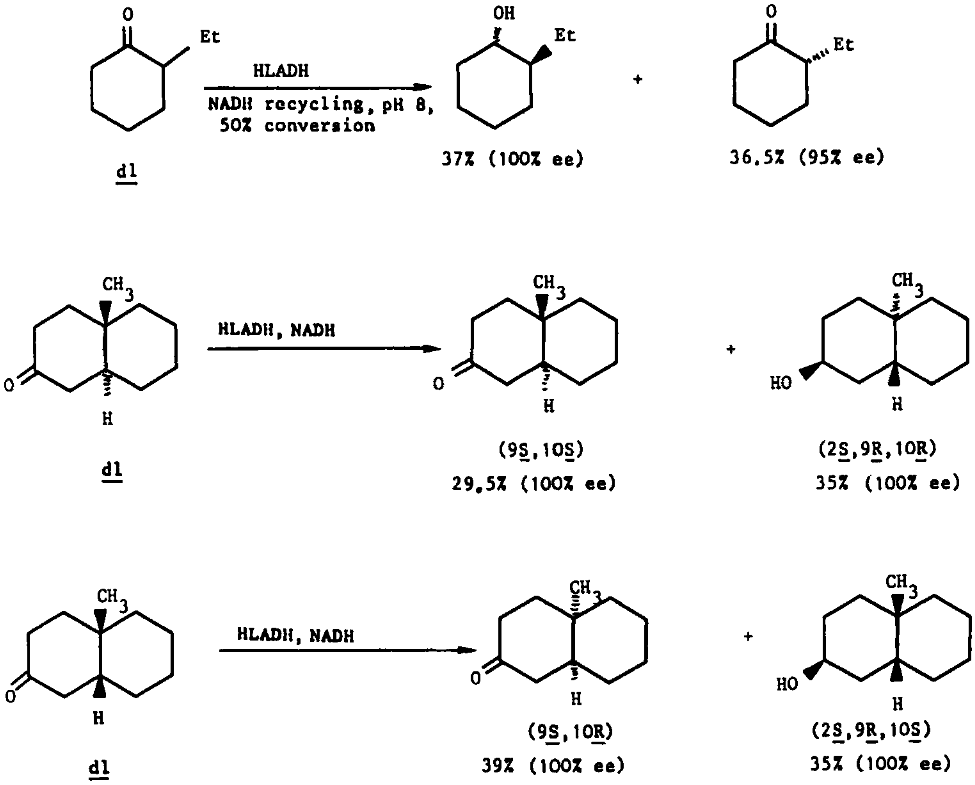
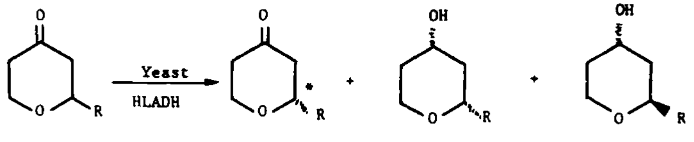

dl
HLADH
NADH recycling, pH 8, 50% conversion
37% (100% ee)
36.5% (95% ee)
dl
HLADH, NADH
(9S,10S)
29.5% (100% ee)
(2S,9R,10R)
35% (100% ee)
dl
HLADH, NADH
(9S,10R)
39% (100% ee)
(2S,9R,10S)
35% (100% ee)

Figure 17. Some examples of HLDAH-catalyzed kinetic resolution of ketones (71).

The best documented of these is HLADH (horse liver alcohol dehydrogenase), an extremely versatile enzyme with well-defined and predictable enantiomer and diastereoface stereospecificities (106). Moreover, it operates on a broad structural range of aldehyde, ketone, and alcohol substrates. A few representative examples are given in Figure 17, which could be exploited preparatively (71). Reduction of heterocyclic 2-alkyltetrahydropyranyl ketones **54** with HLADH produced the optically active unreacted ketone in 31–41% chemical yield and 85–88% e.e. (107).

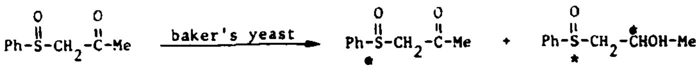


dl-**54** **54**

R	Recovered **54** % yield (% ee)
Me	31 (85)
Et	32 (88)
iPr	41 (86)

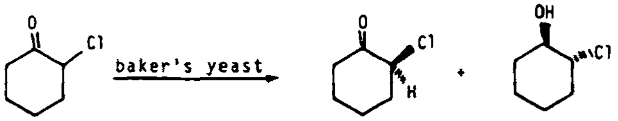
Reduction of the 1-(phenylsulfinyl)acetone **55**, catalyzed by fermenting yeast (*Saccharomyces cerevisiae*), afforded, on 50% conversion, (R_s, S_c)-(+)-1-phenylsulfinylpropan-2-ol (**56**), the unreacted ketone being recovered in pure (*S*)-form. Similarly, the catalyzed reduction of 2-chlorocyclohexanone (**57**) was both enantiomer and diastereoface selective (109).

Oxidation of (±)-*cis*-(3-hydroxyethyl)cyclopentanol (**58**) is both regioselective and enantioselective (110). Optically active bicyclo[3.2.0]hept-2-en-6-one, a useful precursor in prostaglandin synthesis, has been prepared by biological resolution of the racemic compound with yeast (110).

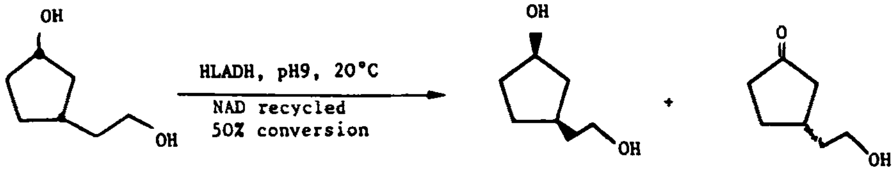


$$Ph\text{-}\overset{O}{\overset{\|}{S}}\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}Me \xrightarrow{\text{baker's yeast}} Ph\text{-}\underset{*}{\overset{O}{\overset{\|}{S}}}\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}Me + Ph\text{-}\underset{*}{\overset{O}{\overset{\|}{S}}}\text{-}CH_2\text{-}\overset{*}{C}HOH\text{-}Me$$

dl-**55** (S)-**55** (100%ee) (R_S,S_C)-**56**



dl-**57** (R)-**57**



dl-cis-58

(1R,3R)-58
80% (70% ee)

Kinetic resolution constitutes a valuable way to obtain ketones of unusual chirality. For example, 4-C_2-methanotwistanone was enzymatically prepared from the racemic compound in 42% yield and 81% e.e. (111).

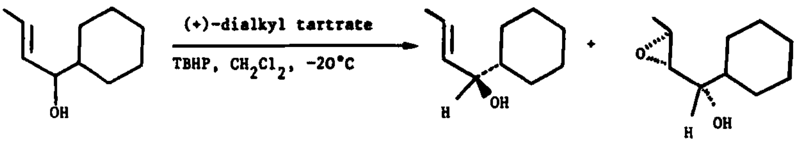
An example of the enzymatic kinetic resolution of an inorganic complex follows: one enantiomer of 1,2,4-triglycinatocobalt(III) is selectively reduced from the racemic mixture using *Proteus vulgaris* (112).

2. *Organometallic and Organic Catalysts*

Kinetic resolutions catalyzed by metal complexes have been reported only recently. Although it was stoichiometric in nature as originally described, the use of the titanium–tartrate complex in the epoxidation of allylic alcohols (Sharpless' reaction) is included in this section because a catalytic version is now known and is being actively developed. A few types of kinetic resolution processes operating on racemic substrates have been described that involve optically active transition metal catalysts other than titanium complexes as chiral auxiliaries. Up to now, these reactions have not been of practical or general value. However, the high enantiomer selectivities shown in some of these reactions, and their catalytic character, deserve attention.

a. Kinetic Resolution of Allylic Alcohols. Asymmetric Epoxidation. This section deals with epoxidation using the titanium tartrate–hydroperoxide system (Sharpless' kinetic resolution).

Soon following their report of an efficient method for the asymmetric epoxidation of primary allylic alcohols (113) with the $Ti(Oi\text{-}Pr)_4$/tartrate/*t*-butyl hydroperoxide (TBHP) system, Sharpless and co-workers disclosed that the same system could be used for kinetic resolution of secondary allylic alcohols (132). The mechanistic and synthetic aspects of the asymmetric epoxidation have been thoroughly reviewed (114–118). The efficiency of the resolution is related to the relative reaction rates ($k_R/k_S = \mathbf{s}$) of the fast- and slow-reacting enantiomers. Among various factors, **s** is dependent on the steric bulk of the tartrate ligand. For the representative example given in eq. [26], **s** values have been shown to be 19, 36, and 104 for dimethyl



tartrate (DMT), diethyl tartrate (DET), and diisopropyl tartrate (DIPT), respectively (114).

In reactions designed with kinetic resolution as the objective, 0.6 equivalent of hydroperoxide is used to ensure that most of the faster-reacting isomer is converted to the epoxide. Another alternative is to use >0.6 equivalent of hydroperoxide. However, in this case, the degree of conversion of the allylic alcohol must be monitored for optimal resolution. A 1:1.2 ratio of titanium to ligand has been recommended by Sharpless (116). An important feature is that the stereochemical outcome of the reaction can be predicted. Of the two enantiomers drawn as Figure 18, the fast-reacting one will have the -OH group below the plane when L-(+)-tartrate is used. Moreover, the absolute configuration of the *p*-bromobenzoates of the resolved alcohols drawn as shown in Figure 19 is correlated with a negative CD (119).

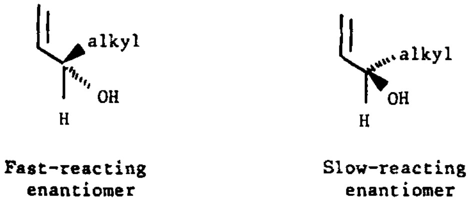


Figure 18. Stereochemical preference when using L-(+)-tartrates (113).

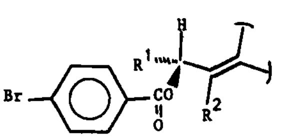


Figure 19. Enantiomer that shows a negative CD (119).

In contrast, the kinetic resolution process has shown lower activity and stereoselectivity for (Z)-allylic alcohols, particularly when the C-4 substituent is an aryl or a secondary alkyl group (12).

Table 6 summarizes some of the data on allylic alcohols successfully resolved by asymmetric expoxidation. Results for an acetylenic carbinol are

Table 6

Available Data for e.e. or **s** Factor in Some Kinetic Resolutions of Allylic and Acetylenic Alcohols with (+)-DIPT-Ti(O*i*Pr)$_4$-TBHP

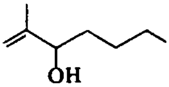
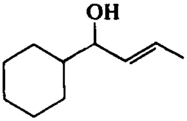
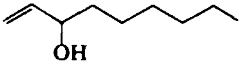
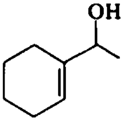
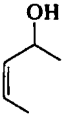
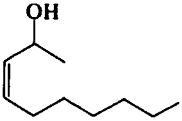
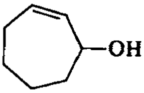
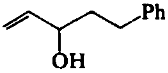
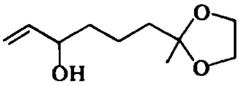
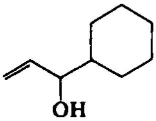
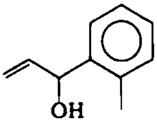
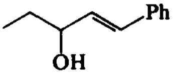
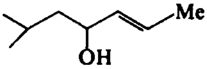
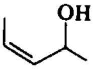
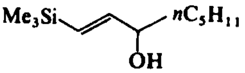
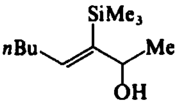
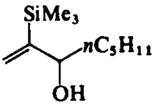
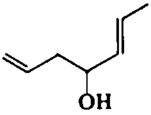
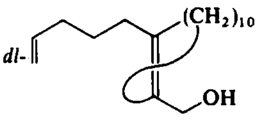
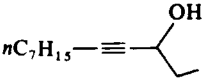
Alcohol[a]	Selectivity (**s**) Factor	e.e. (%)	Reference
	138	>96	12
	104	>96	12
	83	>96	12
	83	>96	12
	~20	91	12
	16	82	12
	16	80	12
	>15		115
	>15		115
	>15		116

Table 6 (Contd)

Alcohol[a]	Selectivity (s) Factor	e.e. (%)	Reference
	>15		119
	>15		115
	>15		116
	16		12
 Me₃Si nC₅H₁₁ OH		>99	122
 SiMe₃ nBu Me OH		>99	123
 SiMe₃ nC₅H₁₁ OH		87	123
		72	124
		>95	125
		21	115

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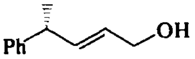
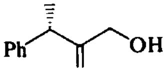
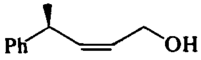
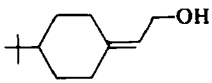
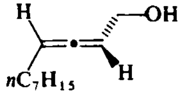
[a] The configuration of the slow-reacting, recovered alcohol is *R*; isolated yields for recovered alcohols range from 30–45%.

Table 7
Kinetic Resolution of Allylic Alcohols in Which Chiral Element Is Not Carbinol Center [with (+)-DIPT][a]

Slow-Reacting (Recovered) Enantiomer	e.e. (%)	Configuration of Recovered Alcohol
	6	*R*
	95	*S*
	80	*S*
	70	
	40	

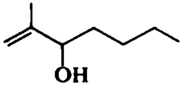
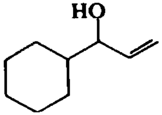
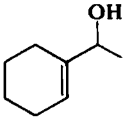
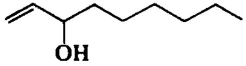
[a] Reactions run to 60% conversion. From ref. 115.

included. In Table 7 some examples of the resolution of chiral primary allyl alcohols are summarized, where the chiral element is not the carbinol carbon center.

Kinetic resolution can be carried out under catalytic conditions (down to 5% titanium–tartrate), the reaction time being increased to attain the same conversion as in the stoichiometric cases. For some substrates, however, the use of catalytic amounts of titanium tartrate is not convenient in terms of chemical yields. Possible reasons for the unsatisfactory results are catalyst inactivation by the substrate, or the titanium-catalyzed opening of the epoxides with formation diol ether inhibitors (120). The effects of variation of reaction stoichiometry, concentration of reactants, and preparation and aging of the catalyst and tartrate have been thoroughly discussed (121). Representative examples of catalytic kinetic resolutions of secondary alcohols are gathered in Table 8.

b. Rhodium-Catalyzed Hydrogenation of *β*-(Hydroxyalkyl)Acrylates. Although homogeneous hydrogenation of olefinic substrates catalyzed by

Table 8
Catalytic Kinetic Resolution of Allylic Alcohols[a]

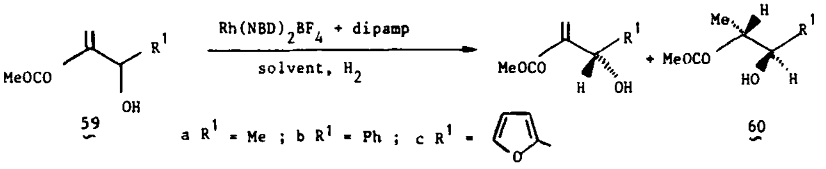
	(+)-DIPT[b]			(+)-DCHT			(+)-DCDT		
	Conversion (%)	Yield[c] (%)	e.e. (%)	Conversion (%)	Yield[c] (%)	e.e. (%)	Conversion (%)	Yield[c] (%)	e.e. (%)
	54	79	88	53	99	93	54	75	93
	60	96	84	63	99	86	63	99	95
	60	93	88	57	99	90	58	94	83
	51	92	86	55	91	98	66	99	98

[a] General conditions: −20°C; 10% $Ti(OiPr)_4$; 15% tartrate ester; 0.6 equivalent TBHP in isooctane in the presence of 3-Å sieves. From ref. 121.

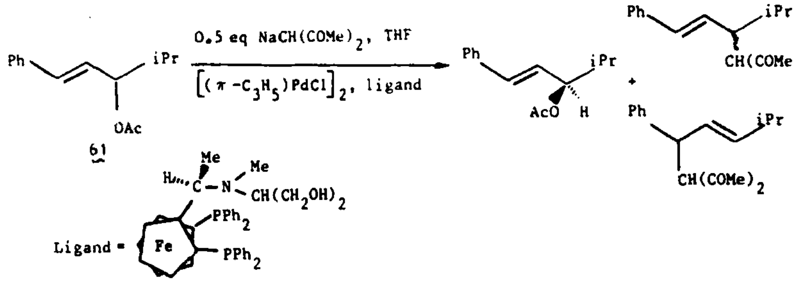
[c] Isolated yield based on percentage of conversion. All recovered alcohols have *R* stereochemistry.

[b] DIPT = diisopropyl tartrate; DCHT = dicyclohexyl tartrate; DCDT = dicyclodecyl tartrate.

transition metal phosphine catalysts has been widely studied, the kinetic resolution of racemic substrates by such a process has been reported only recently. The hydrogenation of β-(hydroxyalkyl)acrylates **59** catalyzed by cationic rhodium–dipamp (dipamp = (*R*, *R*)-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane) has been shown to be both enantiomer- and diastereoface-selective (28). At 20°C, the rate ratio $\mathbf{s} = k_R/k_S$ for hydrogenation of **59a** is 4.5, it is 6.5 at 0°C in THF as solvent. Moreover, **60** was obtained as the sole stereoisomeric hydrogenation product. Analogous results were obtained in the kinetic resolutions of **59b** and **c**, which could be recovered in 90% e.e. (70% conversion).

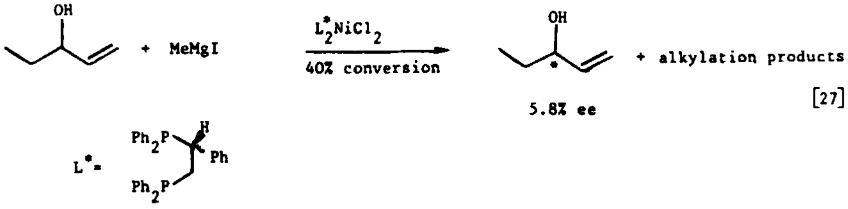

MeOCO
R1
OH
59
Rh(NBD)2BF4 + dipamp
solvent, H2
MeOCO
R1
H OH
+ MeOCO
Me
H
R1
HO H
60
a R1 = Me ; b R1 = Ph ; c R1 =
O

c. Palladium-Catalyzed Alkylation of Allylic Acetates. 1-[(*E*)-styryl]-2-methylpropyl acetate (**61**) was kinetically resolved in its reaction with sodioacetylacetonate in the presence of a chiral ferrocenylphosphine–palladium catalyst (126). In the reaction performed with 0.5 equivalent sodioacetylacetonate, 58% of the substrate could be recovered in 56% e.e. On the basis of this result, the enantioselectivity was calculated to be $\mathbf{s} = k_S/k_R = 14$. From these results, the recovered substrate was predicted to show e.e. >99% on 67% conversion. Actually, on 80% conversion, the acetate **61** was recovered


Ph
iPr
OAc
61
0.5 eq NaCH(COMe)2, THF
[(π-C3H5)PdCl]2, ligand
Ph
iPr
AcO H
Ph
iPr
CH(COMe)2
+
Ph
iPr
CH(COMe)2
Me
Me
H
C
N
CH(CH2OH)2
PPh2
Fe
PPh2
Ligand =

with >99% e.e. The scope of this resolution with regard to structural variations on the substrate has not yet been investigated.

d. Nickel-Catalyzed Coupling Reactions. Kinetic resolution has been observed in a reaction related to the previous one, that is, the alkylation of chiral allylic alcohols with Grignard reagents catalyzed by nickel–phosphine complexes (127) (eq. [27]). The e.e.'s of the unreacted substrate were low, however (<2%).


OH
+ MeMgI
L*2NiCl2
40% conversion
OH
+ alkylation products
5.8% ee
L* =
Ph2P
H
Ph
Ph2P

[27]

The reaction of racemic alkyl Grignard reagents such as **62** and **63** with vinyl bromide catalyzed by an optically active nickel catalyst leads to kinetic resolution of the organometallic reagent (128) (Figure 20). The enantiomeric composition of the Grignard reagents was evaluated after their carboxylation into acids (Table 9).

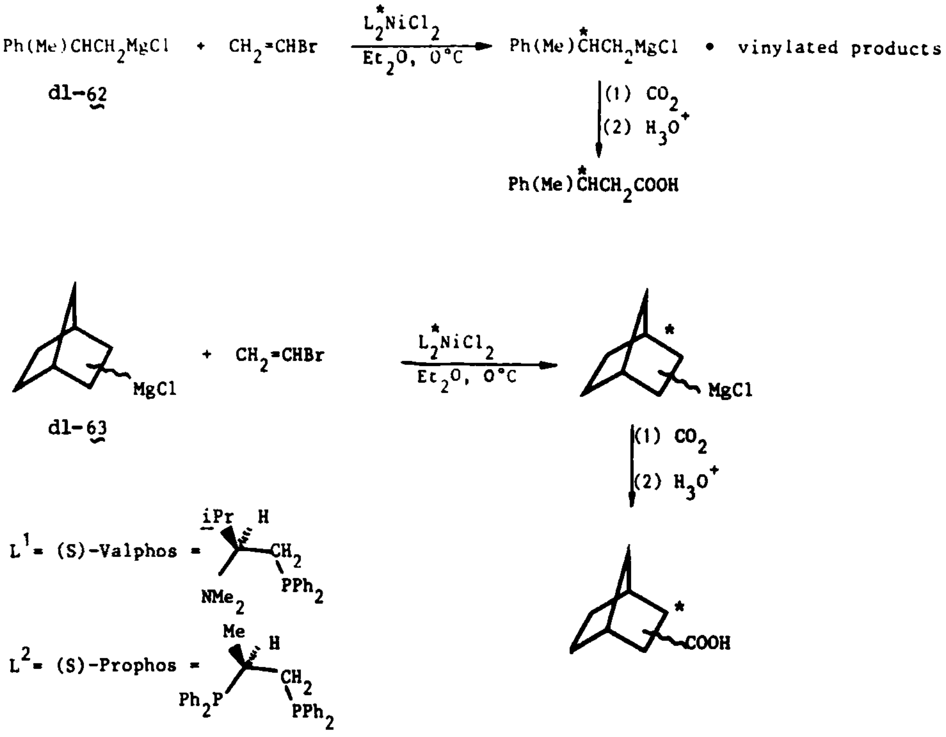

Ph(Me)CHCH2MgCl
+ CH2=CHBr
L*2NiCl2
Et2O, 0°C
Ph(Me)C*HCH2MgCl
+ vinylated products
dl-62
(1) CO2
(2) H3O+
Ph(Me)C*HCH2COOH
MgCl
+ CH2=CHBr
L*2NiCl2
Et2O, 0°C
*
MgCl
dl-63
(1) CO2
(2) H3O+
*
COOH
L1 = (S)-Valphos =
iPr
H
CH2
PPh2
NMe2
L2 = (S)-Prophos =
Me
H
CH2
Ph2P
PPh2

Figure 20. Kinetic resolution of Grignard reagents (128).

Table 9
Data for Kinetic Resolution of Grignard Reagents in Nickel-Catalyzed Coupling Reactions[a]

Grignard Reagent	Ligand L	Conversion (%)	Acid % e.e. (configuration)	Selectivity Factor **s**
62	L^1	41	5.8 (*R*)	1.25
62	L^2	38	1.9 (*S*)	0.93
63	L^1	38	15 (1*R*, 4*S*)	1.9
63	L^2	19	7 (1*R*, 4*S*)	2.0

[a] From ref. 128.

e. Rhodium-Catalyzed Hydroacylation of a Pentenal. In the hydroacylation of the (*R*,*S*)-2-methyl-2-phenylpent-4-enal catalyzed by [Rh(*S*,*S*-chiraphos$_2$]Cl, the unreacted aldehyde was recovered in a high e.e. (129).

f. Rhodium-Catalyzed Isomerization of an Allylic Alcohol. Isomerization of 4-hydroxy-cyclopent-2-enone into 1,3-cyclopentanedione takes place with a **s** factor of 5 when catalyzed with [Rh[(*R*)-binap](CH$_3$OH)$_2$]$^+$ClO^{4-} (R. Noyori, private communication).

g. Kinetic Resolution of α,β-Unsaturated Ketones Using a Chiral Amine-Catalyzed Thiol Addition. 5-Methyl-2-cyclohexen-1-one has been resolved by reaction with thiophenol (molar ratio enone–thiophenol 1.5:1.0) in the presence of catalytic amounts of cinchonidine. The unreacted enone demonstrated 59% e.e. and an *S* configuration (130).

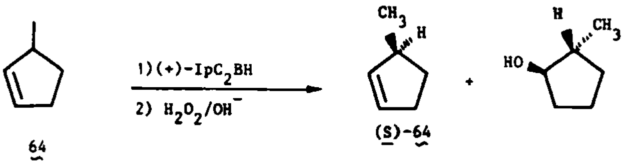
h. Kinetic Resolution of Sulfilimines under Amine Catalysis. *S*-Methyl- and *S*-ethyl-*S*-*p*-tolyl-*N*-tosylsulfilimines undergo kinetic resolution in their reduction with arenethiols under catalysis with optically active amines (131).

i. Enantioselective Hydrolysis of Phenylalanine Derivatives. A perfect enantiomer discrimination (**s** > 1000) has been reported in the hydrolysis of racemic *p*-nitrophenyl *N*-dodecanoyl phenylalaninate, as a result of catalysis with a tripeptide (Z-Phe-His-Leu). The reaction takes place in a medium composed of a double-chain surfactant (ditetradecyldimethylammonium bromide) and a cationic, anionic, or nonionic micellar surfactant. The enantioselectivity was strongly dependent upon the coaggregate system composition (132).

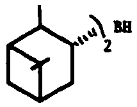
B. Stoichiometric Reactions

1. *Olefins*

The kinetic resolution of alkenes was performed as early as 1962, when Brown reported that hydroboration of a racemic alkene with a deficient amount of optically active hydroborating agent led to the accumulation of the less reactive olefinic enantiomer, the other being transformed into the corresponding borane (133). An example is the reaction of racemic 3-methylcyclopentene (**64**) with a 0.8 mole equivalent of (+)-IpC_2BH (diisopinocampheylborane) that leaves (*S*)-(−)-64 in 30% e.e. (134, 135). 3-Ethylcyclopentene was obtained with the same borane in 37% e.e. Although trans alkenes usually react slowly with IpC_2BH, racemic *trans*-cyclooctene could be resolved with this reagent with an enantiomeric enrichment of 20% (136). Other resolutions were less successful (137).

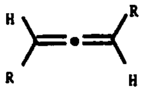


IpC_2BH =



2. *Allenes*

In 1968 Waters and Caserio described the first partial resolution of racemic 1,3-disubstituted allenes (**65**) through reaction with a deficient amount of IpC_2BH (138). Later Moore carried out a systematic study of the kinetic resolution of 1,3-disubstituted allenes of various structures (139). A number of other allenes have been partially resolved by this method: 1,2-cyclononadiene (140), 2-phenyl isobutylidenecyclopropane (141), *trans,trans*-2,8-*trans*-bicyclo[8.4.0]tetradecadiene (142) and spiro[3.3]hepta-1,5-diene (143).



65

a R = Me, Ph
b R = Et, n-Pr, t-Bu

3. *Alkyl Halides*

Racemic secondary alkyl iodides (**66**) and chlorides have been partially kinetically resolved at low temperature (−60° to −70°C) through reaction with 2 molar equivalent of chiral lithio-oxazoline (**67**) (Figure 21) (144). Some results are collected in Table 10. The reaction is believed to proceed via a clean S_N2 process. This was shown by performing the reaction with organic halides of known e.e. and configuration, and by looking at the absolute configuration and e.e. of the acid produced after hydrolysis. If the reaction is properly carried out (with no racemization of the residual alkyl halide), the

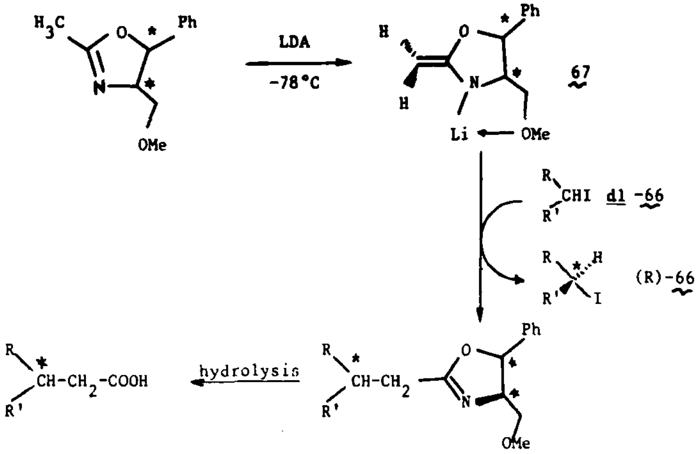


Figure 21. Kinetic resolution of alkyl halides with a chiral lithio oxazoline (144).

Table 10
Kinetic Resolution of **66** with Lithio-oxazoline **67**[a]

(+)-**66**		Recovered **66** (% e.e.)
R	R′	
Me	Et	34
Me	*n*-Pr	30
Me	*n*-Bu	49
Me	*n*-Hex	31
Et	*n*-Bu	46

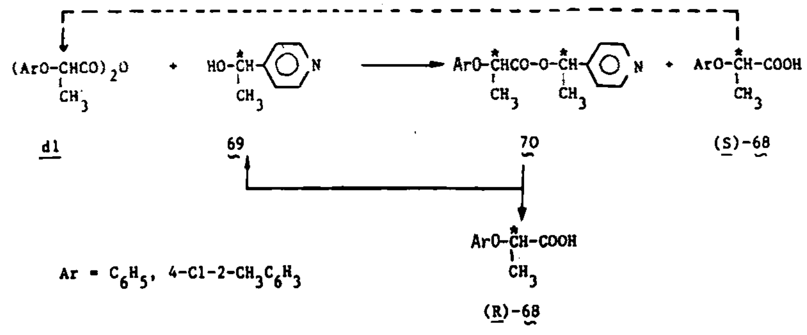
[a] From ref. 144.

maximum specific rotation of one reaction product (halide or acid) can be predicted or checked, provided the rotation of the other is known.

4. Acids

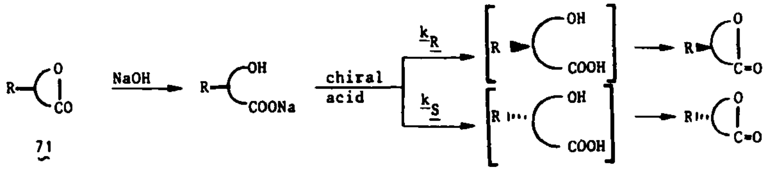
Kinetic resolution of racemic acids via their anhydride can be accomplished with optically active alcohols. As in Horeau's method (Sect. IV-A), this process is useful for the selection of alcohols leading to high stereoselectivity in the kinetic resolution of acids, and for the determination of the absolute configuration of chiral acids. (+)-Endo-*cis*-bicyclo[3.3.0]oct-7-en-2-ol has been used for this purpose (145).

Some preparative aspects of the kinetic resolution of acids with optically active alcohols have been reported. As an example, the herbicidal 2-(aryloxy)-propionic acids (**68**) (Ar = phenyl; Ar = 4-chloro-2-methylphenyl) are prepared through resolution of their racemic anhydrides by optically active 1-(4-pyridyl) ethanol (**69**). Optically active (*R*)-**68** in 70–90% e.e. are obtained by hydrolysis of the esters **70**, whereas (*S*)-**68** were recovered, racemized, and transformed back to the anhydride for a further resolution step (146). These examples are illustrative of the quantitative transformation of the racemic acid **68** into that enantiomer which is economically important, using **69** as optically active material, through a kinetic resolution process. This procedure has been applied to the preparation of the important nonsteroidal antiinflammatory agent naproxen (147).



5. Lactones

A rather general method has been reported for the resolution of chiral lactones **71** by enantioselective kinetic protonation of the corresponding hydroxycarboxylates with chiral acids (eq. [28]) (148).



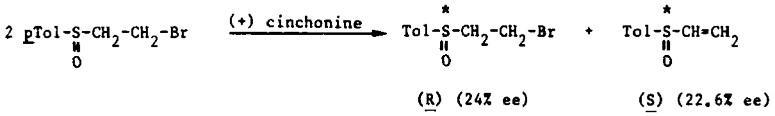
[28]

6. *Sulfoxides*

An efficient kinetic resolution of racemic sulfoxides takes place in the Pummerer-type reaction with optically active α-phenylbutyric acid chloride in the presence of *N*,*N*-dimethylaniline (149).

Kinetic resolution of racemic sulfoxides has been carried out by reaction with optically active poly[*N*-(1-phenylethyl)iminoalanes]. The extent of chiral recognition has been studied according to the structure of the reducing agent, the temperature, and the conversion. Optical enrichments up to 70% have been recorded (15).

Enantioselective oxidation of racemic sulfoxides with optically active oxaziridines was achieved with recovery of unreacted sulfoxides in up to 22% e.e. (150). Partially resolved sulfoxides (up to 24% e.e.) are obtained by an elimination reaction between *β*-halogenoethyl aryl sulfoxides and an insufficient amount of a chiral base (151) (eq. [29]).



$$2\ p\text{Tol-}\underset{\overset{\|}{O}}{S}\text{-CH}_2\text{-CH}_2\text{-Br} \xrightarrow{(+)\ \text{cinchonine}} \text{Tol-}\underset{\overset{\|}{O}}{\overset{*}{S}}\text{-CH}_2\text{-CH}_2\text{-Br} + \text{Tol-}\underset{\overset{\|}{O}}{\overset{*}{S}}\text{-CH=CH}_2$$

(R) (24% ee) (S) (22.6% ee)

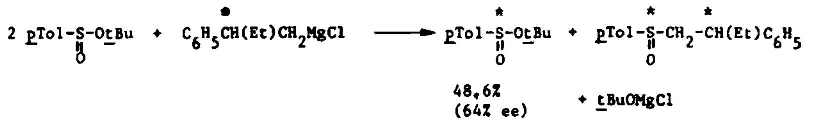
[29]

The reaction of the carbanion derived from racemic methyl *p*-tolyl sulfoxide with (−)-menthyl carboxylates (152) or (−)-menthyl (*S*)-arenesulfinates (153) afforded an enantiomeric enrichment of the unreacted sulfoxide.

Additional processes for the kinetic resolution of sulfoxides may be found in ref. 154.

7. *Sulfinates and Sultines*

The low-temperature reaction of a racemic sulfinate or sultine with a limited amount of a chiral Grignard reagent affords optically active sulfinates with up to 64% e.e. (155) according to eq. [30]. More recently, sulfinates have been resolved with a chiral complex formed between *t*-butylmagnesium chloride and a chiral amine (quinine or quinidine); e.e.'s approaching 30% were achieved (156).



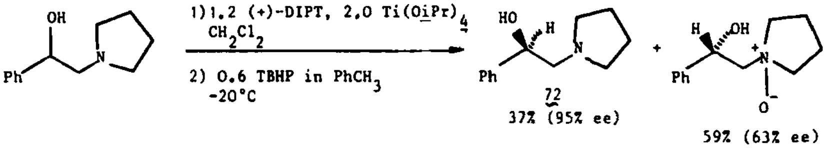
$$2\ \underline{p}Tol-\underset{O}{\overset{}{S}}-O\underline{t}Bu + C_6H_5\overset{\bullet}{C}H(Et)CH_2MgCl \longrightarrow \underline{p}Tol-\underset{O}{\overset{*}{S}}-O\underline{t}Bu + \underline{p}Tol-\underset{O}{\overset{*}{S}}-CH_2-\overset{*}{C}H(Et)C_6H_5$$

$$\underset{(64\%\ ee)}{48.6\%} \quad + \underline{t}BuOMgCl$$

[30]

8. *β-Hydroxyamines*

The kinetic resolution of *β*-hydroxyamines can be carried out by the selective oxidation of one enantiomer to the *N*-oxide with *t*-butyl hydroperoxide (TBHP) and a chiral reagent prepared by mixing two parts of titanium tetraisopropoxide and 1.2 parts of either (+)- or (−)-diisopropyl tartrate (DIPT). An example of this reaction is shown in eq. [31] (157).



[31]

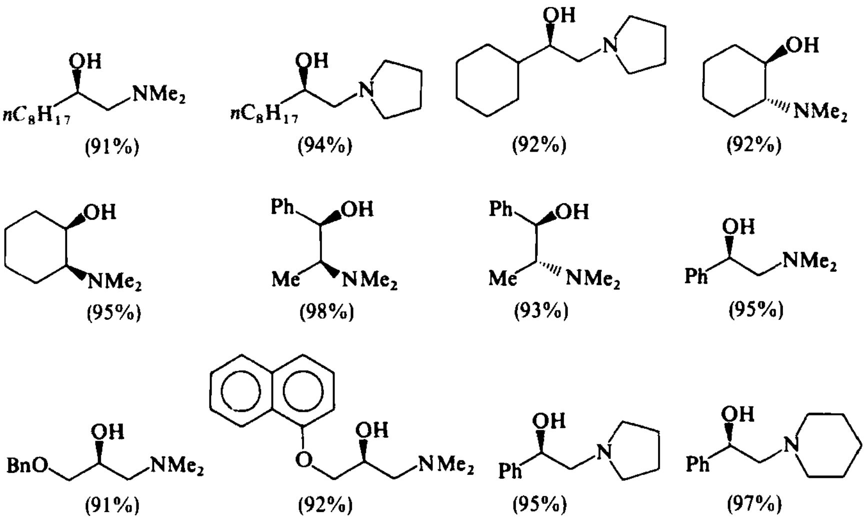
The *N*-oxide product and the unreacted amino alcohol can be separated by taking advantage of their different solubility properties, so that chromatographic separation could generally be avoided. In Table 11 results are collected for compounds that were obtained in 90% e.e. by kinetic resolution of the racemic compounds with the use of (+)-DIPT on 60% conversion of substrate. The e.e. of the recovered substrate is dependent on the nature of the substituents. The structural requirements at the nitrogen atom are important. Primary and secondary amines are not properly oxidized by this system. The "aging" period of the reagent, the titanium–tartrate ratio (the optimum ratio is substrate-dependent), and the amount of water present are parameters influencing the selectivity.

The absolute configuration at the carbinol center of the slow-reacting enantiomer could be predicted and is related to the arrangements of the substituents as drawn for enantiomer **72** in eq. [31].

9. *Phosphines*

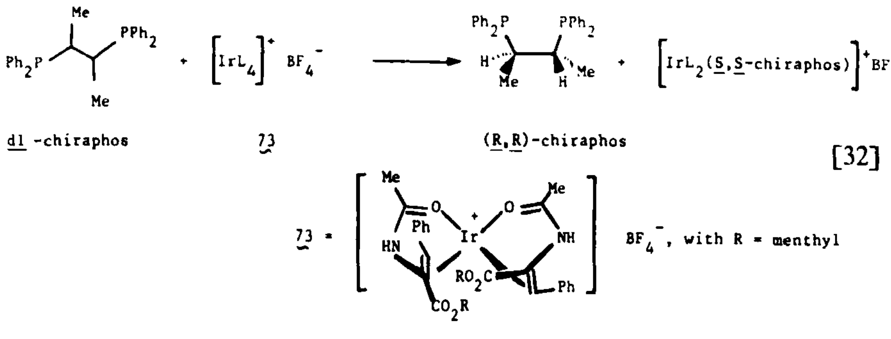
Owing to the development of catalysis by chiral transition metal complexes for asymmetric synthesis, there is an increasing need for chiral ligands. An

Table 11
Slow-Reacting Enantiomers Recovered in Kinetic Resolution of Racemic β-Hydroxyamines by Enantioselective *N*-Oxide Formation[a]


(91%)
(94%)
(92%)
(92%)
(95%)
(98%)
(93%)
(95%)
(91%)
(92%)
(95%)
(97%)

[a] From ref. 157.

example of the kinetic resolution of a ligand followed by its *in situ* utilization was recently given by Brown et al. (eq. [32]): the chiral complex **73** effects kinetic resolution of racemic chiraphos by enantioselective exchange of ligands. The enantiomeric purity of the (*R*,*R*)-chiraphos remaining in the solution was estimated through formation of a rhodium complex and comparison of the enantioselectivity shown by this complex in a hydrogenation reaction with that of the catalyst with optically pure chiraphos (158). This


dl -chiraphos
73
(R,R)-chiraphos
[IrL2(S,S-chiraphos)]+BF4-
73 =
BF4-, with R = menthyl

[32]

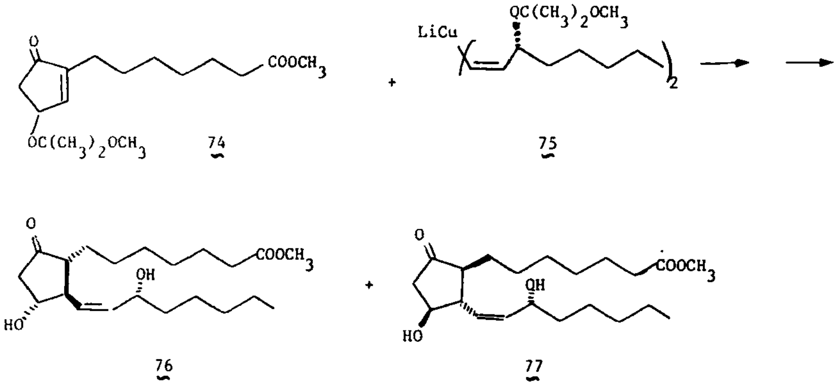
resolution process has been also applied to racemic *trans*-1,2-bis(diphenylphosphino)cyclohexane.

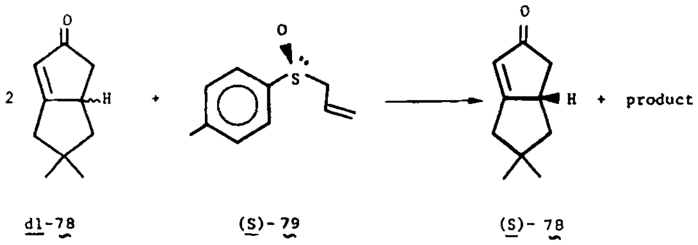
10. Amines; alcohols

The kinetic resolution of amines and alcohols by optically active acid anhydrides is of little preparative value. Such resolutions have rather been used for the prediction of the absolute configuration of these compounds (see Sect. IV-A).

11. α,β-Unsaturated Ketones

Two recent reports exemplify the use of kinetic resolution in synthesis. Kinetic resolution of the racemic cyclopentenone **74** with 3 equivalents of (*S*)-**75** afforded, after deprotection, 30% of unreacted (*S*)-**74**, along with a 86:14 ratio of the diastereomers **76** and **77** (159). Conversely, the diastereomer **76** was obtained as the sole product of the reaction of *dl*-**74** with 3 equivalents of the optically active cuprate (*R*)-**75** (160). In the course of the synthesis of (+)-pentalene, Hua described the preparation of (−)-(*S*)-7,7-dimethylbicyclo[3.3.0]-2-octen-3-one (**78**) in 45% yield by kinetic resolution of





the racemic substrate with (*S*)-allyl *p*-tolyl sulfoxide (**79**) (161). Here the useful compound is the product obtained by combination of one enantiomer of the starting material with the chiral reagent. Because of the high **s** value, the racemic substrate (present in excess) plays the role of a "reservoir," containing the desired enantiomer.

IV. KINETIC RESOLUTIONS OF MECHANISTIC INTEREST

Kinetic resolutions are not basically different from various types of asymmetric syntheses in their principles, since both involve chiral recognition [enantiomer differentiation rather than face or topos differentiation (6b)]. Consequently, kinetic resolution has always been closely related to developments occurring in the fields of stereochemistry and chirality. Some aspects of kinetic resolution not primarily oriented toward preparative chemistry are presented in this section.

A. Assignment of Absolute Configuration

In 1961 Horeau proposed a method for the assignment of the absolute configuration of secondary alcohols (162). This method is based on the kinetic resolution of racemic α-phenylbutyric acid (present in excess), and can be performed on a small scale. Following the hydrolysis of residual anhydride, α-phenylbutyric acid is cleanly recovered. The empirical rule depicted in Figure 22 was proposed by Horeau and is of very high predictive value. When (−)-*R*-α-phenylbutyric acid is obtained, the alcohol has the absolute configuration indicated in Figure 22. In the scheme L is a more "bulky" group than M.

Several hundred examples concerning the Horeau method support the rule given above. A review article was published by Horeau in 1977 (163). Not only is the sign of the residual α-phenylbutyric acid informative, but also its enantiomeric composition. An optical yield of the kinetic resolution has been

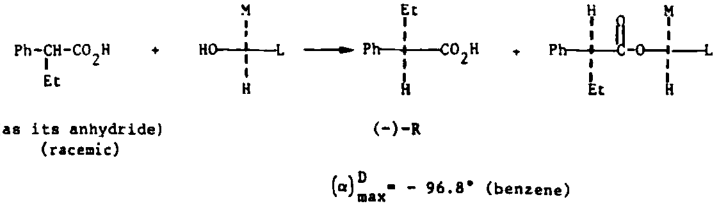


Figure 22. Horeau method for the determination of absolute configuration of secondary alcohols (31, 44).

defined by Horeau; it takes into account the initial molar ratio of racemic anhydride to alcohol and the esterification yield. It is calculated by dividing the specific rotation of the α-phenylbutyric acid recovered after hydrolysis by the specific rotation of the same acid that would have been produced had the reaction proceeded with complete stereoselectivity. Under normal circumstances, reactions are carried out with 1 equivalent of alcohol and 2 equivalents of α-phenylbutyric anhydride. If esterification proceeds to completion and if the esterification is fully stereoselective, the optical purity of the recovered α-phenylbutyric acid will be 33% (specific rotation of 32.3°). This number results because 2 mole of racemic acid are produced in addition to 1 mole of optically pure acid, because one starts with 2 equivalents of racemic anhydride. For details concerning the material balance in the asymmetric esterification of chiral alcohol by a racemic anhydride, see refs. 162 and 163. The optical yield defined as above does not change very much with the extent of reaction or the molar ratio of reactants (163) and is an approximation of the $(\mathbf{s}-1)/(\mathbf{s}+1)$ factor. The actual chiral acylating species is not the anhydride (which contains equal amounts of meso and threo diastereomers) but an acylpyridinium ion which enters into various equilibria (163). The higher the optical yield, the more certain is the absolute configuration assignment.

Menthol and *t*-BuCH(OH)Me give optical yields close to 50%, while the value drops to 8.5% with the more symmetrical EtCH(OH)Me. In the series ArCH(OH)R, the aromatic group has to be considered as L and the alkyl group R as M. It is interesting to point out that the Horeau method can be applied to deuterated alcohols R*CH(D)OH and $CH_3{}^*CH(CD_3)OH$ (164). Optical yields are close to 0.5% (with the **s** factor ≈ 1.01) and are easy to measure because of the high specific rotation of α-phenylbutyric acid. Absolute configurations of the deuterated alcohols RCH(D)OH are found by adopting the steric sequence $R > H > D$ (L,M,S).

The Horeau method also safely applies to chiral amines (except primary amines). However, satisfactory results were obtained in all cases when an acylating agent prepared from α-phenylbutyric acid and imidazole was used (165).

Because of the importance of the Horeau method, the stereoselectivity factors of various acylation reactions with α-phenylbutyric anhydride have been measured (often from the ratio of diastereomeric products). The stereoselectivity factors usually are lower than 5 (163, 165, 166). Data concerning **s** factors (whose numerical value can be as large as 10) in acylation with several types of acids can be found in the literature. See, for example, refs. 145 and 164–168.

An interesting modification of the Horeau method is the assignment of absolute configuration to the enantiomers of a racemic alcohol (163, 169). The reagent is optically active α-phenylbutyric anhydride with racemic alcohol taken in excess. Residual alcohol is recovered and its specific rotation measured. The general rule given above by Horeau allows one to predict the absolute configuration of the unreacted alcohol.

The absolute configurations of the enantiomers of racemic sulfoxides R–S(O)–R′ have been assigned by kinetic resolution using optically active α-phenylbutyryl chloride (0.8 mol equivalent) as the reagent. Part of the sulfoxide is destroyed by a Pummerer reaction. The recovered sulfoxide is optically active (with e.e. up to 40% and with **s** factors close to 2.5, depending upon the structure). A stereochemical model has been proposed to correlate the absolute configuration of residual sulfoxide to that of the acylating agent (149).

Most kinetic resolutions having a broad scope and high **s** factors may in principle be used to assign absolute configurations on an empirical basis (see Sect. III-A-1 and 2).

B. Determination of Maximum Specific Rotations

The use of kinetic resolution methods for calculating maximum specific rotations, when one has in hand racemic or partially resolved compounds, has been fully reviewed and discussed by Schoofs and Guetté (170). This topic is not developed here and the reader is advised to consult ref. 170 for particulars. The basic principle is that, during the analysis of a kinetic resolution, enough information becomes known to permit the extrapolation of $[\alpha]_{max}$ from $[\alpha]$ of the recovered compound at some stage in the kinetic resolution. Circularly polarized light has been used as the chiral reagent in kinetic resolutions in order to predict maximum specific rotations or $\Delta\varepsilon$; this subject has been reviewed by Rau (171) (see also ref. 172).

Horeau proposed also to calculate the maximum specific rotation of the enantiomers of a racemic mixture by using two reciprocal kinetic resolutions. For example, a racemic alcohol is first partially resolved with optically active α-phenylbutyric anhydride, and the alcohol thus obtained is used to partially resolve racemic α-phenylbutyric acid (as anhydride). General equations were developed to combine the data of these two kinetic resolutions for calculating $[\alpha]_{max}$ of the alcohol as well as for assigning its configuration (31, 44).

C. Origin and Amplification of Optical Activity on Earth

The origin of optical activity in living systems is a topic that has been debated since the time of Pasteur. Some unusual physical causes for chiral homogeneity have been proposed: circularly polarized light, weak interactions, and parity nonconservation (for a comprehensive review see Chapter 1 of this volume, ref. 173). Kinetic resolution is one process that has been considered for the creation and amplification of chirality. After unsuccessful attempts, including that of Cotton (174), Kuhn in 1929 achieved the first clear-cut kinetic resolution with circularly polarized light (CPL) (7, 175). *N*,*N*-Dimethyl-α-azidopropionamide was isolated with 0.5% e.e. in this way. In 1974 camphor was produced from racemic camphor with 20% e.e. by Kagan et al. (10), and *trans*-2-hydrindanone (with 30% e.e.) could also be obtained using this method (176). As envisaged by Kuhn, the weak stereoselectivity factor associated with CPL is sufficient to ensure high e.e. if the extent of conversion is large enough. This is clearly borne out by both computations (see Sect. II-I) and experiments.

Once the principle of parity nonconservation in the weak interactions had been proposed, there arose the possibility that the two enantiomers of a chiral substance might not have the same energy content and might then react differently with an achiral reagent. Many calculations have been performed to assess the magnitude of this small effect. For this, as well as for a discussion of the origins of biomolecular handedness, see, for example, ref. 177. Yamagata has proposed (43) a long sequence of consecutive stereoselective reactions (kinetically equivalent to a set of consecutive kinetic resolutions; see Sect. II-I) as a way of amplifying the e.e. of a substance. Unfortunately, the multiplicative model thus proposed (where the overall stereoselectivity is equal to the product of partial stereoselectivities) holds only for very small conversions in each step.

Asymmetric polymerization of α-amino acids is one process envisaged for increasing enantiomeric excesses in the reactant or in the peptide (which can be hydrolyzed back to an enantiomerically enriched amino acid). This point has already been discussed in Sect. II-B, as well as the increase in enantiomeric purity when a partially resolved compound reacts with a racemic reagent (see Sect. II-C). Statistical coupling (duplication or triplication, see Sect. II-J-1.) is also a way of increasing the enantiomeric excess. This process can be even more efficient if some kinetic resolution occurs during the coupling.

It is interesting to recall some views expressed by Mills in 1932 (178) on the origin of optical activity. He considered that reactions in living matter occurring between chiral substances of great molecular complexity are likely to be quite stereoselective. Bimolecular reactions with full stereoselectivity will be faster with enantiomerically pure components (reactant *R* and catalyst C_R) than with the same amounts of reactants having a racemic composition. The overall velocity of racemic systems will be lower, as demonstrated below:

$$\text{Homochiral system: } V_R = k_R[R][C_R]$$

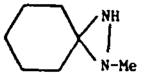
$$\text{Racemic system: } V_{RS} = V_R + V_S = k_R[R'][C_{R'}] + k_S[S'][C_{S'}]$$

Since one must compare transformations of the same amounts of both systems, $[R]=[R']+[S']$, $[C_R]=[C_{R'}]+[C_{S'}]$. Moreover, since $[R']=[S']$ and $[C_{R'}]=[C_{S'}]$ independently of time, $V_R/V_{RS}=2$ since $k_R=k_S$.

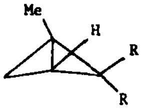
Mills used this conclusion to discuss the growth of a tissue that is not completely racemic in composition (mixture of *d*- and *l*-systems with $d>l$). He showed that in the new tissue the *d*-system will largely predominate (with respect to the composition of the old tissue). This qualitative discussion is based on the hypothesis of a strong mutual kinetic resolution. Calculations such as those described in Sect. II should support the hypothesis given above, by providing comparisons for giving conversions of the amounts of products obtained from starting material having varying enantiomeric compositions. Many kinetic schemes involving autocatalysis in combination with asymmetric synthesis and kinetic resolution were developed and it was shown that a small departure from a racemic composition can be amplified so as to reach 100% e.e. (for leading references see in ref. 177).

D. Particular Cases of Resolution

Kinetic resolution is of interest in the first-time optical activation of compounds that are difficult to resolve by standard procedures. In such cases, the attainment of high yields and even of significant enantiomeric enrichment is not essential. For example, chiral diaziridines with asymmetry at nitrogen were obtained for the first time in optically active form through kinetic resolution with a chiral acid chloride; an e.e. up to 63% was obtained in the case of **80** (179). The kinetic resolution of sulfoxides or sulfinates with some chiral reagents is of mechanistic interest (150, 156).



80



81

The direct resolution of *trans*-1,2-dimethylcyclopropane was achieved by Johnson et al. (180), as described in Figure 23.

Kinetic resolution by chiral ligand L* occurs at the stage of platinacyclobutane. Separation of *trans*-1,2-dimethylcyclopropane from the residual complex is possible [with e.e. up to 35% when L* = (+)-diop]. The dimethylcyclopropane of opposite configuration is obtained (31% e.e.) after treatment of the complex with PPh_3. Gassman et al (181) achieved the kinetic resolution of racemic bicyclo [1.1.0]butanes using RhCl(diop). Achiral products were obtained (by ring opening) as well as residual **81** with 35% e.e. (C = 73%) when R = Ph. This corresponds to a **s** factor close to 1.7.

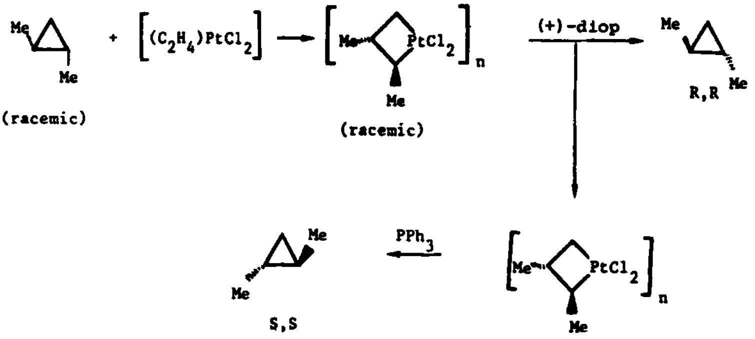


Figure 23. Kinetic resolution of *trans*-1,2-dimethylcyclopropane (180).

Partial photodecomposition of a racemic mixture with circularly polarized light is a method that allows one to obtain for the first time partially enantiomerically enriched compounds for the study of their chiroptical properties; for a review and recent examples see refs. 171 and 172. Stereoselectivity factors are inferior to 1.2–1.3 in these processes, but high extents of conversion give compounds with reasonable enantiomeric purities. This method permits the resolution of structures devoid of functional groups (carboxyl, amino, or hydroxy) that are classically used for resolution by formation of diastereomeric products.

E. Kinetic Isotope Effects

A sensitive method for the determination of kinetic isotope effects is based on kinetic resolution and polarimetric measurement (182). A dextrorotary compound (+)-A is mixed in equimolar amount with its isotopically labeled enantiomer (−)-A*. The desired reaction with an achiral reagent is then performed, transforming A and A* into achiral products. Kinetic isotope effect will induce optical activity in the reaction mixture. Knowledge of the maximum optical rotation of the reaction mixture allows one to calculate the rate constant ratio k/k^*, which is indeed equal to the stereoselectivity factor **s** of a kinetic resolution. As discussed in Sect. II-A, at $t_{\max}$ the ratio A/A* is equal to **s**. Factor **s** can be obtained from the equation $\alpha_{\max} = [\alpha][(+)A]_0[\mathbf{s}^{\mathbf{s}/(1-\mathbf{s})} - \mathbf{s}^{1/(1-\mathbf{s})}]$ where $[(+)\text{-A}]_0$ is the initial concentration and $[\alpha]$ is the specific rotation of enantiomerically pure A. When $[\alpha]$ is high enough, this method becomes very sensitive.

F. Determination of Very Low Enantiomeric Excesses

In 1977 Schoofs and Horeau showed that it is possible to perform a quite accurate enantiomeric analysis of secondary alcohols that are very close to the racemic composition (183). The method depends on the existence of a sufficiently large stereoselectivity factor **s** (> 1.5) during esterification of the alcohol with racemic α-phenylbutyric anhydride. Following hydrolysis, the enantiomeric excess (P) of α-phenylbutyric acid is measured by polarimetry. It was demonstrated that the e.e. of alcohols could be accurately calculated by means of the relationship e.e. $= P(2N - 1)/\mathbf{s}$, where N is the molar ratio between the number of reacting anhydride molecules and the number of alcohol molecules esterified; N can be evaluated by acidimetric titration. The **s** factor was measured by GC analysis of diasteromeric esters. The method was successfully checked on many alcohols of e.e.'s between 0.2 and 1%.

V. CONCLUSION

Kinetic resolution is of interest to many fields of chemistry. This chapter could not extensively cover all the interesting work that has appeared in the literature under the heading kinetic resolution. It was our intention to draw the readers' attention to the main aspects of kinetic resolution that take place under homogeneous conditions. However, some borderline cases, not detailed above, should be briefly mentioned. One situation involves the combination of a fast racemization coupled to a slower enantioselective transformation giving chiral products P and P′:

$$\mathrm{P} \xleftarrow{k_R} R \rightleftarrows \mathrm{S} \xrightarrow{k_S} \mathrm{P}'$$

In such a kinetic scheme, the product ratio is at all times equal to the rate ratio. This kinetic pattern in which the Curtin–Hammett principle applies is characteristic of many reactions involving a so-called "prochiral substrate," which often consists of a mobile racemic mixture of two enantiomeric conformations. The asymmetric cyclization of diarylethylenes into helicenes under the influence of CPL (184, 185), the asymmetric bromination of cyclohexene (186), and the asymmetric hydrolysis of epoxycyclohexane (187) are a few examples. More difficult to discuss are the multistep reactions at some stage of which an equilibrium between enantiomeric species appears (such as the Horeau method at the stage of acylpyridinium ions). Sometimes the racemization equilibrium is not rapid enough with respect to the rate of the enantioselective reaction (Curtin–Hammett conditions are then not fulfilled) (e.g., see ref. 188). Another peculiar situation is that in which the two enantiomers of a racemic mixture are interconverted with different rate constants:

$$R \underset{k_S}{\overset{k_R}{\rightleftarrows}} S$$

This has been encountered in the photostationary state of some photochemical transformations induced by CPL (171) or with the help of a chiral photosensitizer (189). One starts with a racemic composition and after achieving a photostationary state and termination of irradiation, one recovers a nonracemic composition (without loss of material).

We hope that this review will stimulate further advances in kinetic resolutions, which remain of major importance in the chemistry of chiral compounds both from fundamental and practical points of view.

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