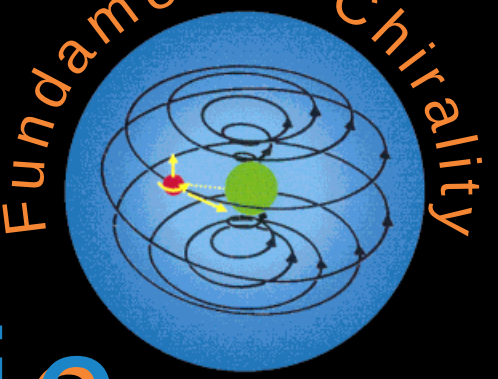
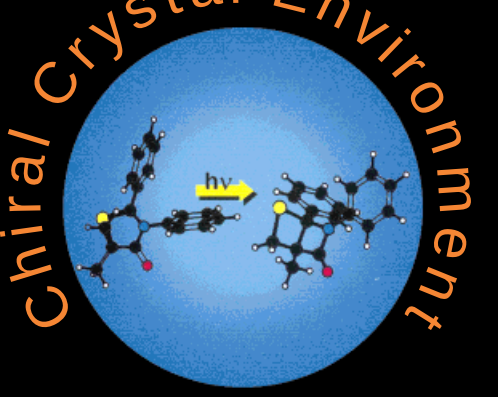
Absolute Asymmetric Synthesis





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Absolute Asymmetric Synthesis: The Origin, Control, and Amplification of Chirality

Ben L. Feringa* and Richard A. van Delden

Dedicated to Professor Hans Wynberg

One of the fundamental and intriguing aspects of life is the homochirality of the essential molecules. From the early days of stereochemistry, the origin of chirality in biological systems has been a challenge to the chemical sciences and numerous theories and experiments have been reported. Despite the great progress in asymmetric synthesis, there are only a few genuine absolute asymmetric syntheses known today. Novel approaches based on the interplay of molecular biology, organic chemistry, and supramolecular sciences have resulted in synthetic molecules that show amplification, autocatalysis, or self-replication and these systems are pertinent to the question as to how to amplify a small stereochemical bias. In this review absolute asymmetric synthesis—including many failures towards this goal—will be discussed with the emphasis on photochemistry with circularly polarized light and conversions in chiral crystals. Amplification mechanisms through autocatalytic systems, liquid crystalline materials, and polymers will also be described.

Keywords: asymmetric amplification · asymmetric synthesis · autocatalysis · chirality · circularly polarized light

1. Introduction

"*…do not let your left hand know what your right hand is doing, so that your giving may be a secret…*"

Matthew 6:3

Most confrontations with chirality (Greek: χείρ (cheir) = hand) in daily life, such as putting on one's shoes or shaking hands, enjoying the taste of an artificial sweetener in a soft drink, or admiring the right-handed spiral of a snail or the bindweed in the garden, go unnoticed. Although there is no apparent direct relationship between this macroscopic chirality and chirality at the molecular level it is generally accepted that homochirality of the essential molecules is one of the most fundamental aspects of life on the Earth.[1]

The sugars such as deoxyribose and ribose in DNA and RNA, respectively, that contain and transfer the genetic information are all right-handed and the 20 amino acids (except for glycine) that form the proteins that are essential for the structure and chemical transformations in cells also share a common relative configuration.[2] Without uniform chirality in the monomeric units that build the biopolymers, the enzymes that catalyze the chemical conversions in the organism and the numerous chiral compounds that are involved in recognition or information processing, such as hormones, current life forms could not exist. The realization of the essential role of supramolecular chirality (and the information content) associated with the DNA helix or the α-helix of proteins makes it difficult to comprehend how the biopolymers composed of D and L monomers could function.

Despite the fact that 150 years have past since Louis Pasteur conducted his famous experiments on the resolution of tartaric acids[3, 4] the origin of chirality in biomolecules is still one of the great current mysteries.[5, 6] The fundamental problems with the generation of asymmetry at the molecular level as well as the expression at the supramolecular and macromolecular level are usually associated with the quest for molecular evolution and the origin of life.[7] Homochirality is thus displayed at the molecular level with large terrestrial excesses of L-amino acids and D-sugars over their enantiomers. The questions as to where biomolecular chirality, or rather biomolecular homochirality, originates from and at what stage in the evolutionary process homochirality took over, have however not yet been answered.[5–8]

Several theories have been proposed that explain the chirality of biomolecules on physical grounds. Attempts to mimic the terrestrial chemical composition at a prebiotic stage

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on a laboratory scale do not show any evolution of homochirality whatsoever, because of the short time scales studied and also because of the difficulties associated with these type of experiments.[9] A model system for the scrutineous experimental demonstration of the naturallike selection of L-amino acids and D-sugars remains to be developed.[10] Nevertheless, despite a good mechanistic knowledge, many attempts were, and are increasingly, made to imitate nature's ability to induce homochirality from scratch. Pasteur tried to grow chiral crystals in a magnetic field following Faraday's discovery of magnetically induced optical activity.[11, 12] The negative results did not discourage him from trying related experiments, such as attempts to induce optical activity by performing reactions in a centrifuge or even rotating growing plants, to modify the optical activity of natural products that were produced. Although all these attempts failed to form enantiomerically enriched products from achiral precursors, he stressed the essence of optical activity and molecular dissymmetry for life and beyond:

"*L'univers est dissymétrique*"

With the stereochemical analysis of Le Bel and Van't Hoff as a basis,[13] it was Emil Fischer who demonstrated that a "dissymmetric force" is not required to generate optically active molecules in living organisms.[14] It was shown that the asymmetry inherent in an optically active molecule can control the asymmetry in subsequent reactions and the proposal was made that in the conversions of chiral compounds the "lock and key" principle provides a mechanism for stereochemical selection in nature.[15] Despite the fact that with this landmark achievement the transfer of chiral information within one molecule or from one molecule to the other is rationalized, it did not provide answers to the following questions: a) what is the origin of the biomolecular chirality; b) why is there a chiral bias for L-amino acids and D-sugars; and c) how can an amplification of an apparently small initial enantiomeric excess be achieved? The formation of enantiomerically enriched products from achiral precursors without the intervention of pre-existing optical activity, namely absolute asymmetric synthesis and the amplification of chirality, is still a challenging opportunity for many scientists.

In this review we summarize the current status of absolute asymmetric synthesis with a focus on recent enantioselective conversions of organic molecules. Excellent reviews and book chapters on various aspects of the origin of chirality in nature and earlier work on absolute asymmetric synthesis and self-replication and amplification have been published.[4–9] Recently, the physical aspects of absolute asymmetric synthesis were reviewed.[16] Herein, main features will be discussed as well as new developments in autocatalysis and amplification mechanisms pertinent to absolute asymmetric synthesis.

2. Chirality in Nature

2.1. Terrestrial Origin

Until 1957 it was thought that nature was symmetric at the atomic level. Biochemical homochirality was therefore assumed to be generated by spontaneous symmetry breaking, with the naturally observed preference for L-amino acids and D-sugars being purely coincidental. An alternative explanation for biochemical homochirality was provided by the

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Richard A. van Delden was born in 1974. He started his studies in the group of Professor B. L. Feringa at the University of Groningen in 1994 on the excited-state properties of chiroptical molecular switches based on sterically overcrowded alkenes. In 1996 he spent six months in the group of Professor M. M. Green, Brooklyn Polytechnic University, performing research on the chiral properties of binaphthalene solubilized in aqueous polymer solutions. On the basis of these projects he received his B. A. in organic chemistry with honors in 1997. In the same year he started a Ph D study under the guidance of professor B. L. Feringa on aspects of chirality in different helical-shaped molecules both in solution as well as in organized media, with the chiroptical molecular switches as a basis. His research interests include physical properties, such as circular dichroism and fluorescence, of organic molecules and organic molecular devices in the broadest sense—from total synthesis to application.

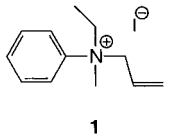
action of an external dissymmetric force and Le Bel and van't Hoff had already made the suggestion of asymmetric photosynthesis through irradiation with circularly polarized light (CPL).[13, 17]

Bonner considers "random mechanisms" and "determinate mechanisms" to distinguish the random generation of either enantiomer of a chiral compound or a process that yields a single enantiomer with a predetermined handedness.[18] But irrespective of the mechanism that created a chiral bias in nature, a fundamental question is at what stage in evolution did molecular asymmetry became a crucial factor. Were primitive life forms, with both D- and L-building blocks available, developed first and did homochirality provide a distinct advantage during the next stage in early biological evolution, or was homochirality a consequence of chemical evolution and a requirement for the evolution of life? In the first case it is conceivable that enantiomorphous primitive life forms could have developed at different places and that in the course of the evolutionary process these became extinct.

It is now generally accepted that homochirality did not have a biogenic origin.[18, 19] Homochirality of the monomers is a prerequisite to form the folded structures of a peptide (for example, the α-helix) essential for the catalytic function of enzymes and the double helix of DNA that is essential for replication. In a number of experiments it has been demonstrated that the formation of oligonucleotides and of polypeptide α-helices only proceed effectively and in a stereoregular manner with enantiomerically pure monomers. For instance, it was recently shown by Eschenmoser et al., using pyranoside nucleotides, that the corresponding tetranucleotide cyclophosphates can assemble into oligomers of 36 nucleotides in length.[20] Oligomers that have the same chirality as the template are exclusively joined leading to a stereoselective oligomerization. When a D-ribopyranosyl unit at any position of the homochiral tetramer was replaced by the corresponding L-unit a reduction in the rate of oligomerization by two orders of magnitude was observed. These findings imply that the "per force" generation of homochiral states is well feasible.

There is considerable experimental evidence for the random generation of optical active organic molecules. Spontaneous generation of optical activity without any chiral bias has been observed in the spontaneous resolution of various racemic compounds and in the preferred crystallization of one of two rapidly interconverting enantiomers from solution.[21] In the first case, the racemic compound forms a conglomerate, that is mixtures of equal amounts of the crystals of the enantiomers.[22] Preferential crystallization of one form or any other mechanism for separation might lead to a certain enantiomeric excess. The normally entropically disfavored generation of optical activity is made possible by the enthalpy gained in going from a homogeneous to a heterogeneous system. It was, for example, shown that $NaClO_3$ forms chiral crystals and when strong stirring was used crystals showing exclusively one optical rotation were obtained.[23]

Preferential enantiomorphic crystallization might result in single enantiomers provided inversion of configuration is fast relative to the rate of crystallization. In a pioneering contribution Havinga described the "spontaneous asymmetric synthesis" in the crystallization of allylethylmethylphenylammonium iodide (**1**).[24] A high bias for one enantiomer was obtained because of a simultaneous interconversion between both stereoisomers in solution. One of the most striking and experimentally useful examples of spontaneous generation of optical activity is the production of enriched binaphthalene (**2**) by suddenly cooling a small portion of its melt, where racemization of the compound is rapid.[25]



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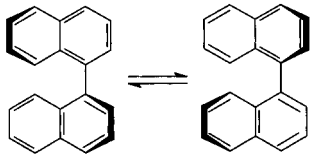

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Spontaneous resolution by chiral crystal formation from achiral molecules has been reported for divinylbenzene, dibenzobarrelene, diacylperoxide, and tri-*o*-thymotide.[26] It should be noted that in all these cases the chiral selection of one of the two enantiomers is purely a matter of chance.

Throughout the years, the stereoselective adsorption of one of the enantiomers of racemic compounds on quartz has been advocated as a mechanism to generate a chiral bias in nature. Many prior results have proved to be erroneous, but the experimental proof for asymmetric absorption of racemic amino acids on quartz was given by Bonner et al.[27] As the abundance of left- and right-handed quartz on the earth is equal, the preferential chiral absorption seems an unlikely mechanism to explain prebiotic homochirality.[28] Of course, this racemic net distribution of terrestrial quartz does not preclude the absolute asymmetric synthesis on a single site.

Despite the fact that these types of mechanisms of spontaneous resolution very inefficiently account for the genesis of materials of nature with a single sense of chirality (for example, no preference for one of two possible enantiomers is expected), the experiments show that a dissymmetric force need not to be present to generate optical activity. Spontaneous chiral crystallization can provide an explanation for biohomochirality. Another possible explanation assumes chiral symmetry exists at the fundamental level and concerns symmetry breaking as a result of an autocatalytic mechanism based on a fluctuating racemic state (see below). One could question whether this would eventually lead to homochirality. It should be noted that recently Siegel reported a paper that places in perspective how natural fluctuations from a perfect racemic state in combination with evolutionary pressures eventually could lead to homochiral molecules.[29]

2.2. Extraterrestrial Origin

In recent years there has been a growing notion that the deposition of nonracemic materials from extraterrestrial origin on the Earth might have been the source that led to the uniform homochiral compounds essential in prebiotic evolution. Most notable in this respect is the isolation of L-alanine with a significant enantiomeric excess from the

Murchison meteorite that landed on Australia in 1969.[30] Recently, optically active α-alkylated (unnatural) amino acids were also isolated from the meteorite, thus providing strong evidence against terrestrial contamination.[31] By combining these findings with the exciting discovery of intense sources of circular-polarized radiation in the cosmos,[32] one realizes that it is highly feasible that asymmetric photolysis of organic material in interstellar clouds produces enormous quantities of optically active molecules. Even if further experimental proof can be obtained, the question of the preferred handedness in nature still remains. For extensive discussions on the extraterrestrial origin of homochirality the reader is referred to several papers and monographs.[5, 6, 18, 33]

3. The Weak Force

3.1. Parity Violation

In 1957 parity violation (namely, a different probability for the occurrence of a process and its mirror image), as proposed by Lee and Yang,[34] was discovered in the weak nuclear force (the fourth type of force, next to gravity, electromagnetism, and the strong nuclear force, through which elementary particles interact with each other).[35] This discovery led to the experimental observation that the β-particles emitted from radioactive nuclei have an intrinsic asymmetry: left-handed (L)-electrons are preferentially formed relative to right-handed (R)-electrons.[36] The major consequence of this finding is that chirality exists at the level of elementary particles. Until the late 1960s it was assumed that parity violation was confined to nuclear reactions, but then a theory was developed that unified the weak and electromagnetic forces.[37] According to this theory, an electro-weak force between the electrons on one hand and the protons and neutrons of an atom on the other, which does not conserve parity, exists (the Z force). It is predicted that the weak nuclear force should be able to discriminate between mirror images not only through the weak charged currents (W force) responsible for the observed nonconservation of parity in β-decay, but also through weak neutral currents (Z force). This situation is indeed found.[38] The W force is zero for (R)-electrons and nonzero for (L)-electrons, while β-decay produces mostly (L)-electrons as shown by experiment (measurements on positrons, the positively charged analogues of electrons, show mostly (R)-positrons being produced).[39] For the Z force, the (L)- and (R)-electrons have charges of opposite sign and nearly equal magnitude. This difference in sign causes (R)-electrons to be attracted to the nucleus and (L)-electrons to be repelled.

Two important consequences of the weak Z force between electrons and nuclei that pertain to our discussion are: a) all atoms are chiral and b) a chiral molecule exists in a lower or higher energy state relative to its enantiomer. This parity violation results in an energy difference between two species, which for practical reasons are considered to be enantiomers. The concept of enantiomers, however, implies precise mirror images and the true enantiomer of a chiral compound is in fact a compound with the opposite absolute configuration that is composed of antiparticles; this compound then has exactly the same energy as the original molecule.[40] There is no fundamental rational as to why chirality at such an elementary level is present.

3.2. Absolute Asymmetric Synthesis Using Fundamental Chirality

A few ways by which the parity violating weak force can cause enantioselectivity, which might eventually pave the way to the origin of biohomochirality, have been proposed, although not supported experimentally.[41] Firstly, the excess (L)-electrons produced by β-decay emit left-handed electromagnetic radiation and this could cause the preferential decomposition of one stereoisomer in a racemate and leave a net excess of its enantiomer.[42] Secondly, β-particles themselves can decompose chiral molecules directly. Calculations as well as experiments,[43, 44] however, showed that enantiomeric excesses of less than one part in 10^9 are obtained with such decompositions. A third possibility would be that the Z force itself affects the production of either D- or L-amino acids by stabilizing one enantiomer over the other. Calculations show that the magnitude of the parity violation energy (E_{pv}, the difference in the parity violation energy between two enantiomeric structures as a consequence of the Z force) is about 5.2×10^{-16} J mol^{-1} for steroid analogue **3** and 1.04×10^{-13} for a 10° twisted ethylene (**4**; Figure 1).[45]

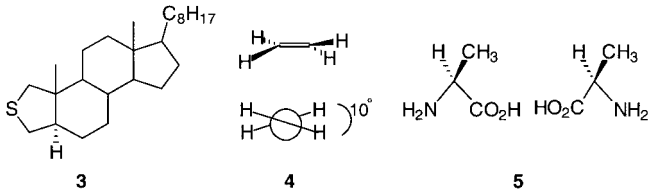


Figure 1. Structures for which E_{pv} has been calculated.

Furthermore a value of 6.5×10^{-14} J mol^{-1} was found for a specific conformation of alanine (**5**) in water with the naturally abundant L enantiomer having the lower energy.[46] An enantiomeric excess of about one in 10^{17} is expected from this energy difference. Although this value is smaller than a random deviation from a racemic state, it is striking that the Z force clearly governs a small bias for the naturally occurring L-amino acid. A direct estimate for the energy difference (E_{pv}) for sugars has not yet been reported, but it should be noted that the naturally occurring D-sugars are chemically correlated to the L-amino acids through the conversion of D-glucosamine to L-alanine.[47]

Some attempts were made to perform absolute asymmetric syntheses (in fact degradation) using the fundamental chirality of β-decay.[48] Initial results of ten different radiolysis reactions with a variety of β-emitters, however, showed no optical activity in the products.[49] These negative results are presumably a result of very low polarization at higher wavelengths since the degree of circular polarization of β-rays falls off with an increase in wavelength.[50] Subsequent experiments with longitudinally polarized electrons from a

linear accelerator showed a slight preference in the degradation of the D isomer of racemic leucine.[51] A chiral discrimination of up to 1.4% is observed. The chirality induced by β-decay will only be significant for absolute asymmetric synthesis if it can be combined with an amplification mechanism (see below). Any future application of these techniques on a laboratory time scale therefore does not seem very likely.

4. Physical Forces

4.1. Absolute Asymmetric Synthesis Using Physical Forces

Numerous attempts to induce absolute asymmetric synthesis using a physical force have been described. Experiments to induce photochemical asymmetric synthesis using linearly polarized light in the presence of a magnetic field were reported as early as 1939.[52] The very low optical yields found in these reactions were however shown to be irreproducible.[53] This actually has been the case all through this century, as no unequivocally absolute asymmetric synthesis using chiral field effects (except for circularly polarized light, see below) has yet been described. Dougherty and co-workers performed absolute asymmetric epoxidations of isophorone using hydrogen peroxide in vessels rotating in the Earth's gravitational field and found optical rotations in the range of $0.001 - 0.017^\circ$.[54] These optical rotations were dependent on the rotation rate of the vessel and were only found when vertical rotations were employed. Clockwise and counterclockwise rotation resulted in opposite optical rotations of the epoxide.

This research group also performed an absolute asymmetric epoxidation of stilbene and a reduction of 1-bromo-1-methyl-2,2-diphenylcyclopropane in a magnetic field oriented in various orientations relative to the Earth's gravitational field that gave optical rotations of maximal 0.01°.[55] Their data were, however, later refuted on theoretical grounds (see below).[56] Later attempts to achieve absolute asymmetric synthesis as well as preferential crystallization in this kind of chiral gravitational field (using strong stirring either clockwise or counterclockwise in the Earth's gravitational field) showed no optical activity in the products.[57] Honda and Hada did find optical activity of a J-aggregate of the 1,1′-diethyl-2,2′-cyanine chloride product in a reaction induced by conical swirling,[58] but the observed optical activity was later attributed to an artifact.[59]

Perhaps the most discussed chiral physical field in the context of potential use in absolute asymmetric synthesis is a magnetic field parallel to an electric field. In 1893 Curie stated that a magnetic field parallel to an electric field appears to generate chirality because the indistinguishable parallel and antiparallel arrangements are interconverted by the operation of parity (space inversion) just like mirror-image forms of a molecule.[60] In 1975 Gerike reported the first example of such an absolute asymmetric synthesis.[61] Six different reactions were tested in both stationary and alternating magnetic and electric fields and all attempts gave some optical rotation that seemed to be opposite in sign for parallel and antiparallel arrangements of the fields, but according to the author this might have been coincidental. Furthermore, the optical rotations that were observed could not be reproduced. Gerike's results were also later rejected on theoretical grounds; no combination of a uniform and constant electric and magnetic field can induce an asymmetric bias into reactions going to completion (see below).[62]

This is only one example of a disputed absolute asymmetric synthesis in magnetic fields. In 1986 Takahashi and co-workers claimed an asymmetric electrochemical reduction in a magnetic field in the case of the conversion of phenylglyoxylic acid into mandelic acid using NADH.[63] An excess of D-mandelic acid (up to 21%, depending on pH) was found in all cases. Surprisingly, this was independent of the orientation of the magnetic field and proportional to the magnetic flux density. As a consequence of the failure of the reversal of the magnetic field to reverse the asymmetric effect (which is completely without theoretical explanation) Bonner decided to try to reproduce these results and was not successful. It was concluded that Takahashi's results must be a result of an experimental artifact.[64]

More recently a spectacular example of an enantioselective reaction in a static magnetic field was reported by Zadel and co-workers.[65] Enantiomeric excesses ranging from 11 up to 98% were claimed in a static magnetic field of 0.43 – 2.1 T for the reactions of aromatic aldehydes and ketones with Grignard reagents and $LiAlH_4$, respectively. It was however unpredictable as to which enantiomer predominated in each experiment. Intrigued by the high levels of enantioselectivity and the simplicity of the asymmetric synthesis using some of the most common organic reactions, several groups engaged in experiments to reproduce the stereoselectivity. All attempts to reproduce these results failed and it turned out that the observed enantiomeric excesses were a result of the deliberate seeding of the reaction mixtures with an optically active compound before work-up.[66, 67]

4.2. Chirality Aspects of Physical Forces

To see whether or not it is possible to perform absolute asymmetric synthesis using physical forces it is necessary to take a close look at the chirality aspects of these forces. In 1977 it was already stated that a simultaneous application of a uniform and constant electric and magnetic field can not affect the equality of the enantiomeric population (50:50) in a racemic mixture at equilibrium.[62, 68] This argument is based on symmetry operations of the system. It appears that even though a colinear arrangement of electric and magnetic fields is chiral in the sense that it has a mirror image in which it is converted by space inversion, both arrangements can also be interconverted by time reversal. In 1986 Barron proposed a more general theory about chirality by stating that there are physical systems that exist as two mirror images yet are not truly chiral in a fundamental sense because dissymmetric systems are not necessarily chiral when motion is concerned.[69] Barron introduced the terms "true" and "false" chirality to indicate time-invariant and time-noninvariant enantiomorphism, where "true" chirality is only possessed by

systems that exist in two distinct enantiomeric states that are interconverted by space inversion but not by time reversal combined with any proper spatial rotation. This distinction is illustrated for a simple system of rotating cones in Figure 2.

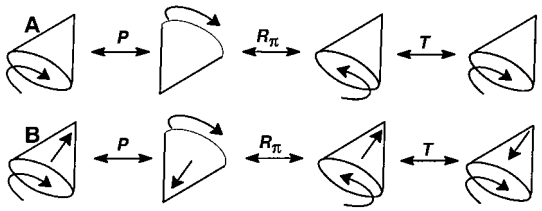


Figure 2. Representation of "True" (B) and "false" chirality (A). (From reference [69].)

A rotating cone (A) exists as two mirror-image states interconverted by space inversion (P). Time reversal (T) combined with a 180° spatial rotation (R) also interconverts these two states, which indicates "false" chirality. When this rotating cone also displays a translation motion (B) along the axis of spin the two mirror-image states that exist are again interconverted by P. In this case, however, a combined application of T and R does not interconvert these two states, which indicates "true" chirality. This explanation is of course not restricted to conical shapes and is valid for all combinations of translation and rotation as long as the translation is along the spin axis.

The same argument holds for a parallel arrangement of an electric field E—a time-even polar vector—and a magnetic field B—a time-odd axial vector. The time-even polar E vector changes sign under space inversion but is time-invariant, while the time-odd axial B vector is time-non-invariant but does not change sign under space inversion (Figure 3). In this case time reversal combined with a 180° spatial rotation has the same effect as space inversion, which indicates "false" chirality.

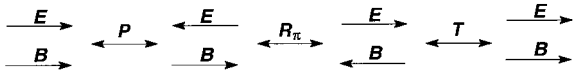
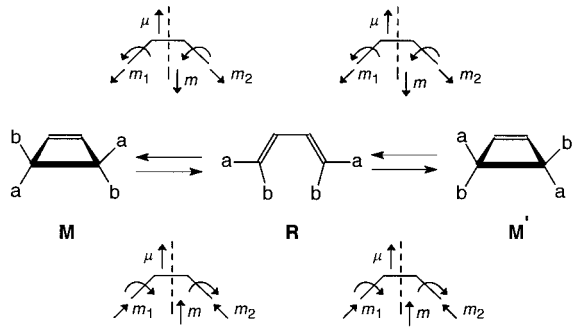


Figure 3. "False" chirality of a parallel combination of a magnetic (B) and an electric field (E).[69]

A crucial distinction between a truly and falsely chiral influence is that only under the former the energy of a chiral molecule will be different from that of its mirror image. Chiral enantiomers will remain strictly degenerate in the presence of a falsely chiral influence.[70] A falsely chiral influence (for example, a colinear electric and magnetic field) can however act as a chiral catalyst since it modifies the potential energy barriers that change the relative rates of formation of enantiomeric products without affecting the equilibrium thermodynamics. In theory, a falsely chiral influence can induce absolute asymmetric synthesis for reactions far from thermodynamic equilibrium. One theoretical example using the breakdown of microscopic reversibility is illustrated below for the conrotatory interconversion of butadiene with two enantiomeric chiral cyclobutenes (Scheme 1).[71] During the entire process the molecule preserves its twofold rotation (C_2) axis. Symmetry arguments show that there will be an electric dipole moment (μ) parallel to this C_2 axis and, to a good approximation, μ will have the same magnitude and sense during the entire process. The rotational motion of the a and b groups will generate transient magnetic moments (m_1 and m_2) parallel to the local rotation axis.



Scheme 1. Relative orientation of the transient electric and magnetic dipole moments during the conrotatory interconversion of a butadiene and two enantiomeric chiral cyclobutenes. (from reference [71].)

From Scheme 1 it can be seen that this magnetic moment (m) is opposite for the forward and back reaction in both cases (R ⇄ M and R ⇄ M′), but the same for the ring closure R ⇄ M and the ring opening M′ ⇄ R and vice versa. An electric field will partially align the molecules while a parallel magnetic field will result in different energies of the antiparallel and parallel rearrangements of μ and m resulting in a potential energy profile as depicted in Figure 4. This system can thus develop an enantiomeric excess during the reaction that is under the influence of a falsely chiral combination of physical fields as long as no thermodynamic equilibrium is established. It should be emphasized however that this is a purely theoretical example; in practice the motion of molecules in solution is isothermal and according to transition-state theory all states are in equilibrium.[72]

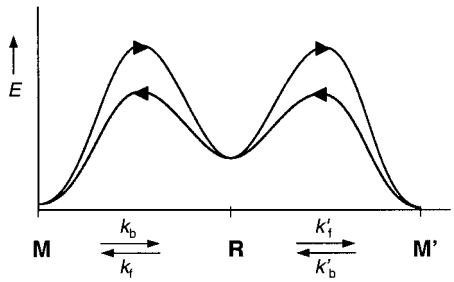


Figure 4. Energy diagram for the conrotatory interconversion of two enantiomeric chiral cyclobutenes (k_f = rate of forward reaction; k_b = rate of back reaction). (From reference [74].)

The enantiomeric excesses formed in a reaction under a falsely chiral influence will ultimately disappear if thermodynamic equilibrium is established. Similarly, a falsely chiral influence cannot generate an enantiomeric excess in a racemic mixture. However, some reservations should be made involving enantio-differentiating reactions in a falsely chiral field since non-uniform fields or forces could be present or the reacting species might be partially aligned on the walls of the reaction vessel.[73] In a thought provoking article entitled "Can a magnetic field induce absolute asymmetric synthesis"

Barron predicted that asymmetric induction might take place in a magnetic field provided the prochiral molecules are pre-aligned (on a surface, in a crystal or at an interface) and the system is far from equilibrium.[74] The experimental proof for such a magnetic field induced asymmetric synthesis still remains an intriguing challenge.

Let us consider the physical forces used in the absolute asymmetric syntheses mentioned above and investigate their chirality. Firstly, linearly polarized light together with a magnetic field will be discussed. A static magnetic field (B) parallel to the direction of propagation of an incident, arbitrarily polarized light beam (k) used in the earliest examples of absolute asymmetric synthesis is, in principle, a truly chiral influence (parallel and antiparallel arrangements of B and k are true chiral enantiomers because they cannot be interconverted by time-reversal since k, unlike E, is time-odd; see Figure 3) and is thus a candidate for asymmetric synthesis.[75] Although the attempted absolute asymmetric synthesis was irreproducible, the truly chiral influence of a magnetic field parallel to the propagation vector of arbitrarily polarized light has been shown experimentally. This combination of forces can induce a difference in the refractive index (magnetic field induced dispersion difference, MIDD) and correspondingly, the absorption coefficient (magnetic field induced absorption difference, MIAD) of enantiomers. The shift, independent of the polarization of the light beam, changes sign either on replacing the chiral molecule by its mirror image or on reversing the relative directions of the magnetic field or propagation direction of the light beam.[76] It should be noted that, because of the very small effects involved, there is no foreseen practical application of MIDD and MIAD.

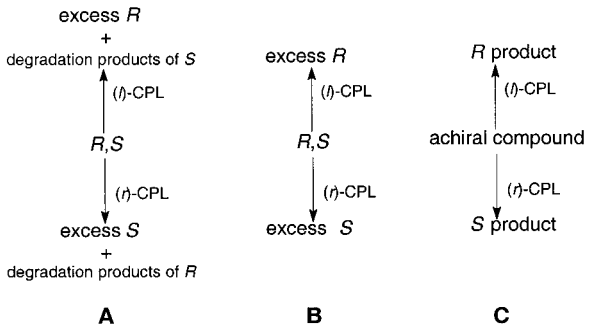
Secondly, rotations in gravitational fields are close analogues of electric and magnetic fields (false chirality). The spinning vessel has a time-odd axial angular momentum vector (such as E), while the gravitational field is a time-even polar vector (such as B); thus the system displays "false" chirality. In this case, an enantiomeric excess can only be established under kinetic control and the enantiomers are strictly degenerate.

Thirdly, a conical swirl is definitely a truly chiral system. Yet no enantiomeric excess in any process is expected as a result of a condition reported in 1930, but often ignored.[77] For an absolute asymmetric synthesis to occur the externally applied truly chiral forces must actually cause the reaction. This means that the applied field must be capable of either changing the rate of the reaction or generate a pair of diastereomeric transition states of different energies that lead to the products. Because of this, absolute asymmetric synthesis using rotating vessels in the Earth's gravitational field can be discarded in advance, irrespective of whether the force field is truly chiral or not.

5. Absolute Asymmetric Synthesis with Circularly Polarized Light

Circularly polarized light (CPL) is without doubt truly chiral electromagnetic radiation in the sense described above and therefore CPL should in theory be able to induce absolute asymmetric synthesis.[78] The only basic requirement is that the molecules to be converted should absorb visible or UV light. Since circular dichroism (CD) arises from a difference $\Delta\varepsilon$ in the absorption of right- and left-circularly polarized light by an optically active molecule, right- and left-handed CPL should preferentially interact with one enantiomer of substances that exhibit circular dichroism. In addition, irradiation of a prochiral molecule with CPL might preferentially convert the ground state of molecules into an excited state with a certain chirality that can lead to a preference for the formation of one enantiomer. Three types of enantioselective conversions effected by CPL irradiations can be distinguished (Scheme 2):

A) Preferential photodestruction in which one of the enantiomers of a racemate is preferentially converted and the other remaining stereoisomer is enriched; this process is irreversible.
B) Photoresolution, namely a deracemization process of photochemically interconvertable enantiomers.
C) Asymmetric photosynthesis, namely an enantioselective photochemical formation of an optically active compound from a prochiral starting material.



Scheme 2. Three ways of using CPL for enantio-differentiating reactions. For further information see the text.

Early work on enantio-differentiating reactions by CPL has been reviewed by Izumi and Tai as well as Inoue.[79, 88] In considering the possibility that CPL can induce biomolecular homochirality we should point out that a very small portion of the light that comes to the earth is circularly polarized, probably as a result of scattering by particles in the atmosphere. Other sources that have been suggested are reflection to surfaces such as quartz crystals. It should be emphasized that there is no chiral bias as a tiny excess of either (l)-CPL or (r)-CPL can be observed depending on the time and place on the earth.[5, 48, 80] Therefore natural asymmetric synthesis with CPL seems to be only a feasible mechanism to generate homochirality if a high local intensity of CPL were created. In such a case a strong amplification mechanism is also necessary to explain homochirality since high *ee* values can only be obtained directly for molecules with high anisotropy factors or optical-rotatory powers, which is usually not the case for biomolecules. Absolute asymmetric synthesis using CPL is certainly interesting from the point of view of laboratory applicability since circularly polarized light is readily generated from linearly polarized light in combination with a quarter wavelength plate.[79, 81]

5.1. Photodestruction

As early as the 19th century Le Bel and Van't Hoff recognized the potential use of (*r*)- and (*l*)-CPL in photochemical reactions for the production of an excess of a particular enantiomer from a racemic substrate.[13] Cotton was the first to test this idea by attempting enantio-differentiating photolysis of an alkaline solution of copper tartrate.[82] It was known that copper tartrate exhibits unequal absorptions for right- and left-handed CPL in the red region of the spectrum. However, no rotation was detected after photolysis owing to insufficient energy of the light employed, as was later shown by Byk.[83] Kuhn and co-workers succeeded in performing an enantio-differentiating reaction with circularly polarized light in the UV region, namely the photodestruction of the racemic dimethylamide of α-azidopropionic acid.[84] In this first unequivocal asymmetric photolysis, the final optical rotation could be correlated very well with the anisotropy factor of the substrate derived from CD experiments.

Soon after this finding a study by Mitchell appeared that reported optical rotation in the product after irradiation of the sesquiterpene humulene with CPL.[85] Enantio-differentiating photochemical reactions employing CPL have, however, not been extensively explored. As photodestruction involves the preferential conversion of one of the enantiomers of a racemate, that is, kinetic resolution, a high *ee* value might be achieved provided the reaction is run to high conversions.

Thus Kagan and co-workers[86] reported optical purities of 20% (Kuhn anisotropy factor $g = 0.09$ at 310 nm; see Section 5.2) for camphor and 30% ($g = 0.24$ at 313 nm) for *trans*-bicyclo[4.3.0]nonan-8-one, at 99% photodestruction of the racemates. These are among the highest stereoselectivities reported so far, but the very low yield of the remaining optically active material is illustrative of the disadvantages associated with this kinetic resolution method.

Although the obtained *ee* values are considerably lower, a very important aspect is the asymmetric photolysis of (*R*,*S*)-leucine using laser-induced circularly polarized UV light,[87] Bonner and co-workers obtained leucine with about 2% *ee* after irradiation of a racemic sample of the amino acid with a circularly polarized laser beam (212.8 nm, 180 J). This direct way of enriching an amino acid is of course of major importance in the study of the origin of biomolecular homochirality.

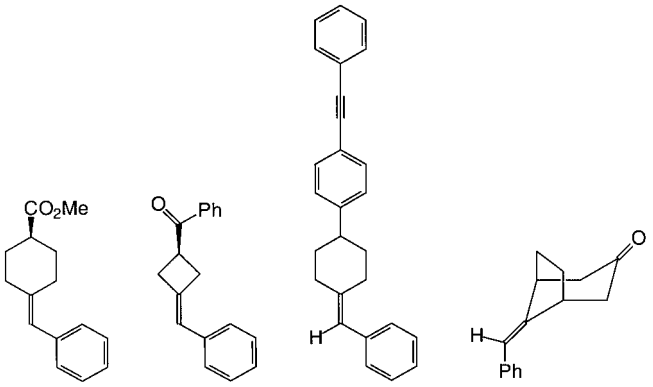
5.2. Photoresolution

Next to photodestruction, partial photoresolution comprises a second mechanism by which enantio-differentiating reactions using circularly polarized light can operate in a reversible manner.[88] For instance, irradiation of racemic chromium oxalate solutions in water with CPL gradually resulted in an optical-rotary power without affecting the chromium oxalate contents.[89] The CPL selectively excites one of the two enantiomers of chromium oxalate and from this excited state racemization takes place, the other enantiomer, which is hardly affected, will accumulate in solution until an equilibrium is reached. Stevenson and Verdieck as well as Norden reported a similar partial resolution of octahedral bidentate Cr^{III} complexes.[90]

In a photoresolution process irradiation of a racemate with (*l*)-CPL will cause the formation of an excess of the *R* enantiomer whereas irradiation with (*r*)-CPL will lead to an excess of the *S* enantiomer (or the reverse enantioselectivity takes place; see Scheme 2). The selectivity that can be expected in such a process is governed by the Kuhn anisotropy factor g where $g = \Delta\varepsilon\,\varepsilon^{-1}$.[91] The enantiomeric excess in the photostationary state (ee_{PSS}) is given by Equation (1). For most compounds the anisotropy factor seldom exceeds 1% and therefore *ee* values below 0.5% are to be expected from CPL photoresolution. Notable exceptions are for instance chiral lanthanide complexes that show g values up to 3% and chiral bicyclic ketones with anisotropy factors of about 1% (see below).

$$ee_{PSS} = \frac{g}{2} = \frac{\Delta\varepsilon}{2\,\varepsilon} \qquad (1)$$

The research group of Schuster has studied a large variety of axially chiral (arylmethylene) cycloalkanes (Figure 5) in their search for a liquid crystal phototrigger based on CPL (see Section 7).[92] Typically, irradiation of methyl ester (*R*)-**6** at 254 nm resulted in complete and selective racemization.



6 **7** **8** **9**

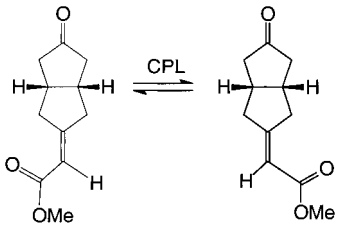
Figure 5. Axial chiral (arylmethylene)cycloalkenes for photoresolution.

This points to a stable system since irradiation of the enantiomerically pure compound should exclusively lead to racemization and no decomposition should occur with a photobistable compound if it is to be suitable for a fully reversible photoresolution experiment. With related compounds this requirement was not always fulfilled and considerable photodecomposition often accompanied photoracemization. Anisotropy factors could be enhanced from $g_{251} = 7.5 \times 10^{-5}$ for **6** to $g_{361} = 10^{-2}$ for ketone **7** by tuning the exciton interactions between the chromophores through structural modifications. Although optically active **7** shows complete racemization in one minute and an enantiomeric excess of 5×10^{-3} was calculated for the photostationary state based on the g factor, no successful photoresolution was described.

In an alternative approach the photoresolvable group was part of the mesogenic compound itself. For this purpose

axially chiral 1-benzylidene-4-(phenylethynylphenyl)cyclohexanes (for example, **8**) were prepared, but again the anisotropy factor g proved to be too small.[93] Slow photoresolution was observed for the axially chiral bicyclo[3.2.1]octan-3-one **9** ($g_{313} = 0.0502$, $ee_{max} = 2.5\,\%$), which led to an enantiomeric excess of 1.6 %.[94]

In 1995 Schuster and co-workers reported the first reversible photoracemizations, that is the reversible formation of an excess of one enantiomer after irradiation of a racemate with CPL.[95] The observed *ee* value was 0.4 %, again using axially chiral bicyclic ketones (Scheme 3). The ketone chromophore exhibits a high g factor since the n-π^* transition is forbidden. The absorption of the substituted acrylic ester moiety **10** has no overlap with that of the ketone group, and the relatively rigid bicyclo[3.3.0]octane skeleton is used to link the chromophores in order to avoid averaging of the CD spectra by strong coupling. These features resulted in a g value of about 10^{-2}. Irradiation of **10** with unpolarized light leads to efficient photoracemization by isomerization around the double bond.



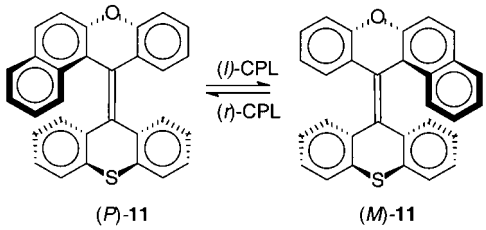
10

Scheme 3. Reversible photoderacemization of a rigid bicyclo[3.3.0]octanone with CPL.[95]

Our interest in the control of chirality by circularly polarized light stems from the challenge to develop a chiroptical molecular switch based on CPL.[96] The switching process we envisioned involves the interconversion of the P and M enantiomers of helical-shaped inherently dissymmetric alkenes. Despite the fact that two enantiomers represent two different states (0 and 1) in a binary system, they have the same properties and switching with light, independent of the wavelength, will result in a racemic mixture. Theory predicts that the ratio of enantiomers in a racemic photoresponsive material can however be modulated by irradiation at a single wavelength by changing the handedness of the light, such as in the examples discussed above. The possible photoisomerization steps are the following (Scheme 4): 1) After irradiation with CPL one of the enantiomers (P or M) will be formed in small excess when one starts with a racemate (M,P). 2) Irradiation with light at one wavelength, but alternating (l)- and (r)-CPL, will result in a modulation between a P and a M helix. 3) The racemic mixture can be obtained again after irradiation with linearly polarized light (LPL).

Scheme 4. Photoisomerizations based on irradiation with circularly polarized light (CPL) and linearly polarized light (LPL).

Out of a large number of sterically overcrowded chiral alkenes that were synthesized and resolved, helical-shaped alkene **11** meets the requirements for a useful switch (Scheme 5). Decisive factors for a successful CPL switch are: 1) a selective interconversion of enantiomers by CPL without any photodestruction; 2) a high g factor; 3) thermally stable enantiomers; 4) a high quantum efficiency for photoracemization, since the rate of photoresolution depends exponentially on this quantity.



Scheme 5. Photochemical interconversion of P (right handed) and M (left handed) helices of **11** upon irradiation with (l)- or (r)-CPL.[96]

The enantiomers of **11** are stable at ambient temperatures ($\Delta G^{\neq}_{rac} = 25.9 \pm 0.2$ kcal mol^{-1}) and fatigue resistant. Stereospecific photoisomerization takes place that reverses the helicity of the molecules. Thus irradiation of (P)-**10** with unpolarized light at 300 nm resulted in rapid photoracemization without notable degradation and with a high quantum yield ($\Phi_{rac} = 0.40$ in n-hexane). Furthermore large CD absorptions and optical rotations, similar to those seen in helicenes, are found, which are useful for detecting the rather small change in chirality upon CPL irradiation.

We took into consideration that for practical purposes the photoresponsive system should exhibit sufficiently large g values at wavelengths above 300 nm. The experimental g value for **11** is -6.4×10^{-3} (313 nm), which indicates that an *ee* value of 0.3 % might be expected under ideal conditions. Irradiation of (P,M)-**11** with (l)-CPL indeed resulted in photoderacemization. Successive irradiation for 30 min with (l)- and (r)-CPL at the same wavelength led to a modulation of the chirality as detected by CD measurements and no deterioration of the CD signal was observed during eight cycles. Typical switching cycles are shown in Figure 6. Switching occurs between photostationary states with small excess of P and M helices and an *ee* value of 0.07 % and -0.07 %, respectively. The *ee* values are smaller than anticipated but by

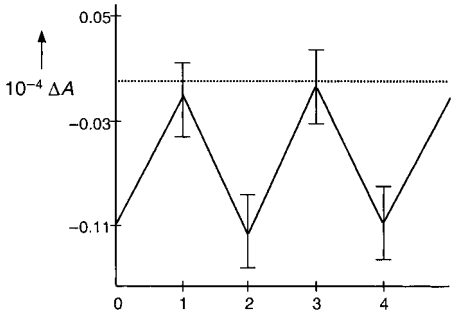


Figure 6. The difference in CD absorption at 313 and 400 nm ($\Delta A_{313} - \Delta A_{400}$) for a solution of **11** in n-hexane after alternating irradiation with (l)- and (r)-CPL at 313 nm.[96]

taking into account that the light is 90% circularly polarized at best and that the band width was 10 nm *ee* values no greater than 0.1 – 0.2 are realistic.

The demonstration of a chiroptical molecular switching process based on photomodulation of helicity using CPL is not only interesting from a fundamental point of view but also offers intriguing possibilities for molecular optical devices, which we briefly mention here. The two forms of the bistable molecule with opposite helicity constitute a memory element in a binary logic system—a requirement for reversible optical data storage. In the system described here, although still a very primitive version, the chirality is modulated and as a consequence so are the chiroptical properties and the three-dimensional structure. The principle of a potential data storage system is depicted in Figure 7. Irradiation of a racemate (*M*,*P*) using (*r*)- or (*l*)-CPL for the writing process generates *P*-enriched or *M*-enriched regions, respectively.

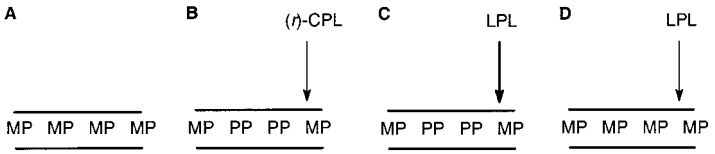


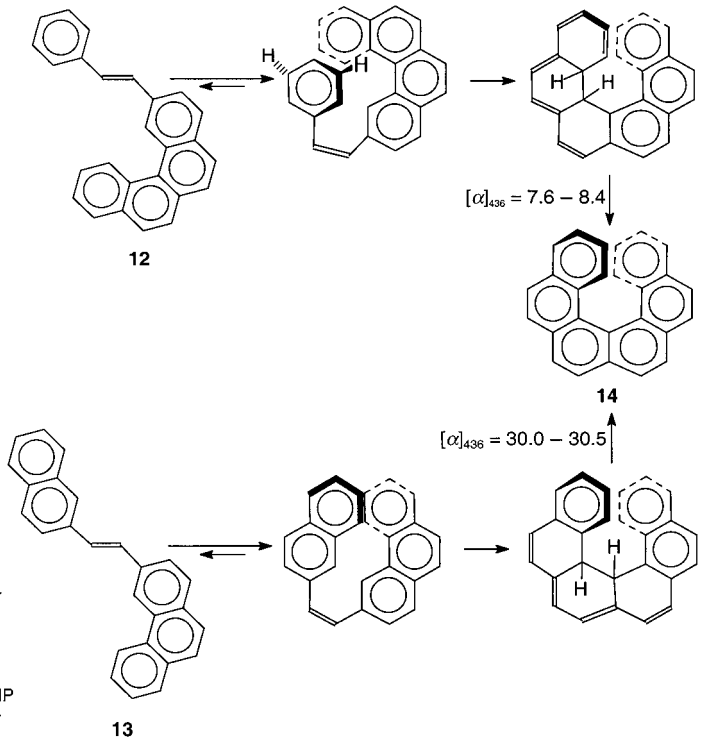
Figure 7. Proposed optical data storage system based on the chiroptical molecular switch **11**. Writing is done with CPL while reading and erasing is done with LPL. A: unwritten; B: write; C: read; D: erase.

Detection (read-out) is achieved with LPL outside the absorption band (for example, optical rotation), whereas written information can be erased by LPL (or unpolarized light) at the original wavelength, which generates the racemate (*M*,*P*) again. In principle, this photoresolution constitutes a three position—(*P*,*M*), *P*-enriched, and *M*-enriched—switch, with the distinct advantage that all switching processes can be performed at a single wavelength merely by changing the chirality of the light.

5.3. Asymmetric Photosynthesis

An early attempt to test the idea of using CPL as a means of performing absolute asymmetric synthesis was an irradiation experiment of an asymmetrically substituted triphenylmethyl radical, but no unequivocal optical activity was observed.[97] Suitable systems to prove the concept of CPL-controlled asymmetric synthesis are helicenes, which are known to have an extremely strong optically rotatory power and are produced by a photochemical ring closure and subsequent oxidation of a diarylethylene in the presence of iodine. Indeed the groups of Kagan and Calvin independently succeeded in a CPL-induced enantioselective synthesis of helicenes (Scheme 6).[98, 99]

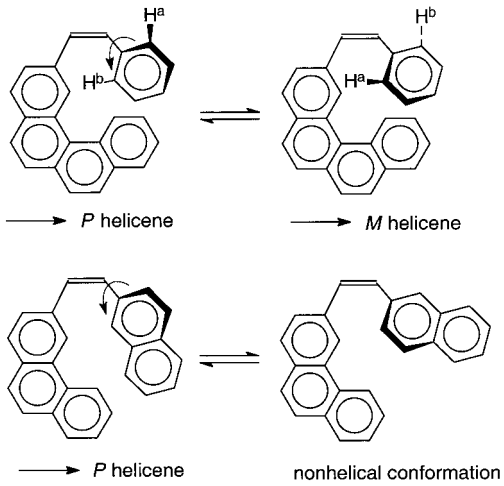
When 1-(2-benzo[*c*]phenanthryl)-2-phenylethylene (**12**) or 1-(2-naphthyl)-2-(3-phenanthryl)-ethylene (**13**) were irradiated with CPL in the wavelength range of 310 – 410 nm optically enriched hexahelicene (**14**) was obtained via a dihydrohelicene intermediate. The optical rotations of the synthesized helicene ($[\alpha]_{436}$) were 7.6 – 8.4 starting from **12** and 30.0 – 30.5 starting from **13** (positive optical rotations were obtained with (*l*)-CPL). Accordingly, 1-(2-naphthyl)-2-(2-benzo[*c*]phenanthryl)-ethylene, 1-(3-phenanthryl)-2-(2-benzo[*c*]phenanthryl)-ethylene and 1,2-bis-(2-benzo[*c*]phenanthryl)-ethylene under the same conditions gave optically active hepta-, octa-, and nonahelicene.



Scheme 6. Absolute asymmetric synthesis of hexahelicene from **12** and **13** using CPL.[99, 100]

A mechanism involving the formation of racemic helicene followed by partial photoresolution was rejected by the observation that photoresolution of racemic hexahelicene gave resolved material with opposite optical rotations compared to the helicene product of the photochemical reaction. Partial photoresolution probably does compete with absolute asymmetric synthesis and as a consequence lowers the optical yield.

The photochemical reaction takes place from the lowest excited singlet state of the *cis* alkene. Circularly polarized light will preferentially excite the ground-state molecules to an excited state with a certain helical sense, which leads to a certain optical rotation in the final product. In this excited singlet state however, rotation around the aryl – ethylene bond requires little energy. In the case of **12**, such a bond rotation would cause equilibration of the two unequally excited enantiomers and therefore result in a decrease in the optical activity of the final product (Scheme 7). A comparable bond rotation for **13** will result in a nonhelical conformation that will not lead to the helicene product and therefore this bond rotation does not influence the enantiomeric excess of the helicene **14** formed. This explains the large difference in optical rotations found for **14** starting with **12** or **13**. Experiments using substituted analogues of **12** confirm this mechanistic rational.

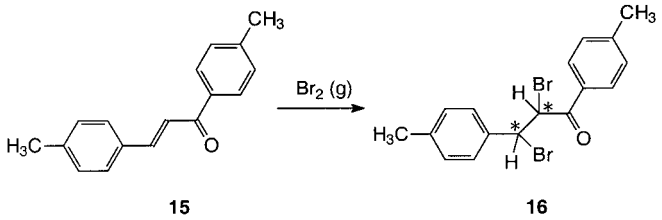


Scheme 7. Effect of bond rotation on the formation of hexahelicene.

6. Photochemistry in Chiral Crystals

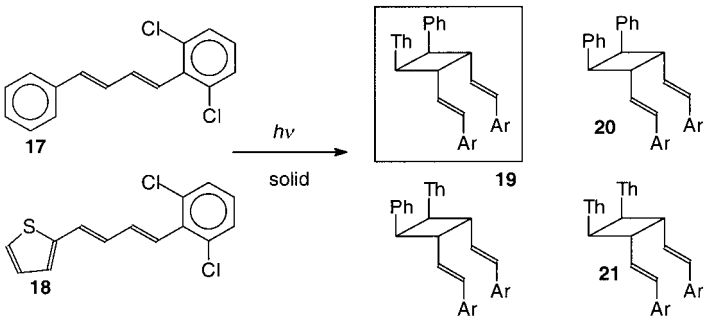
A different approach to absolute asymmetric synthesis is the use of a chiral crystal field in topochemically controlled solid-state reactions. Asymmetric synthesis has been reported by doping achiral compounds in a crystal of a chiral compound and using chiral inclusion phenomena, but this is not an *absolute* asymmetric synthesis.[100, 101] Chiral compounds always crystallize in chiral space groups but also a number of achiral compounds are known to form chiral crystals.[22] Most achiral molecules are known to adopt interconverting chiral conformations (a feature that might have more general implications in asymmetric synthesis than we tend to realize), which could lead to a unique conformation upon crystallization. Green, Lahav, and Rabinovich already noted from a viewpoint of asymmetric synthesis that stereocontrol is exerted during crystallization in the chiral form; it is only necessary to lock the chirality in a configurationally stable product by a subsequent solid-state reaction.[102] Unfortunately, it is not easy to arrange achiral molecules in a chiral form in the crystal. Molecules with a C_2-symmetry axis tend to crystallize in chiral structures, according to Jacques and co-workers, but despite impressive work on crystal engineering, predictions on a correlation between crystal symmetry and molecular structures are still hard to make.[22, 103] The asymmetric crystallization of achiral compounds is stimulated by autoseeding with the first crystal formed. Although the chiral sense of the spontaneously formed crystal cannot be predicted, seed crystals of the preferred chirality can be added in a more practical procedure to obtain one enantiomorph of a crystal. Achiral compounds that crystallize in a chiral one-component crystal form are compiled in the JCPDS crystal data series and the Cambridge Crystallographic Data Centre.[104]

Penzien and Schmidt reported the first absolute asymmetric transformation in a chiral crystal.[105] The enone 4,4′-dimethylchalcone (**15**) was found to crystallize in the chiral space group $P2'2'2'$ with a highly twisted conformation. Reaction with bromine provided the dibromide **16** with optical purities of 6–25% (Scheme 8).



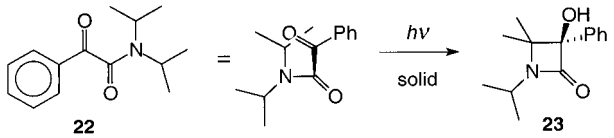
Scheme 8. First example of absolute asymmetric synthesis using the chiral crystal environment of 4,4′-dimethylchalcone.[105]

For early work on the (attempted) asymmetric synthesis in chiral crystals, the reader is referred to a review by and the work of Green, Lahav, and Rabinovich.[102, 106] As detailed discussions on photochemistry in organized media, enantioselective solid-state reactions of the enantiomorphs of chiral crystals, and stereochemistry of solid-state organic reactions have appeared[107] we will restrict ourselves to some recent findings. Photochemical conversions in the solid state are well known and stereochemical control can be excellent. It was found that upon irradiation of homochiral mixed crystals of butadienes **17** and **18** a [2+2] photodimerization takes place yielding heterodimer **19** with an optical yield of 70%.[108] Formation of the achiral homodimers **20** and **21** was prevented by tuning the ratios of heterodimer (**19**) and homodimers (**20** and **21**) by selective excitation of the thiophene derivative. As expected, some crystals gave left-handed and others right-handed cyclobutanes (Scheme 9).



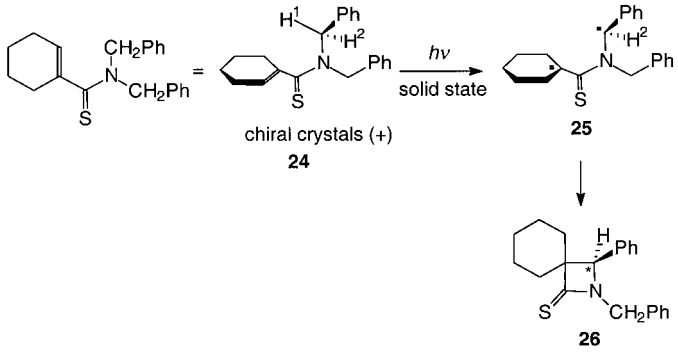
Scheme 9. Enantioselective hetero-dimerization in a two-component homochiral mixed crystal of two butadienes.[108]

Many examples of solid-state photochemical reactions that use the chiral crystal environment of an otherwise achiral compound to induce an optically enriched product have been reported in recent years.[109] A remarkable case—the photocyclization of the diisopropyl amide **22**—was reported by Toda et al. (Scheme 10).[110] A helical conformation is found in the chiral crystal as a consequence of a twisting around the CO–CO bond, and this conformation is locked by photocyclization to afford β-lactam **23** with 93% *ee*. A prominent



Scheme 10. Formation of chiral β-lactam **23** by photocyclization of **22** in the crystal.[110]

example is also the formation of optically active (*R*)-(+)-thiolactam **26** with enantiomeric excesses of 81–97% by intramolecular [2+2]-photocyclization of one enantiomorphous form of achiral α,β-unsaturated thioamide **24** via diradical **25** using the chiral crystal environment (Scheme 11).[111]

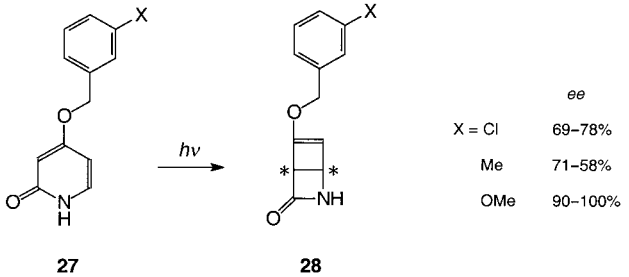


Scheme 11. Absolute asymmetric synthesis by photocyclization of **24** in the crystal.[111]

Although the photocyclization gives a very large enantiomeric excess, a decrease in selectivity is observed at higher conversion (the above mentioned 81% *ee* is obtained after 100% conversion, while 97% *ee* was obtained after 20% conversion). This is attributed to an increased disorder in the packing of the crystal as a result of the accumulation of product and the local melting of the crystals by excess radiation energy.[112] However, no melting was observed after 20% conversion, which resulted in the relatively high *ee* values.

The major drawbacks of the crystal-field method, which prevent it from becoming a general method for absolute asymmetric synthesis, are the unpredictability of the crystallization of the achiral substrates, which as indicated can be circumvented by manual seeding, and the fact that achiral substrates seldomly crystallize in chiral space groups. It was shown that it is possible to regulate this chiral crystallization by crystal engineering. In the case of the formation of the β-lactam (Scheme 12), it was shown that the ability of a compound to crystallize in a chiral space group was increased by using compounds with *meta*-substituted aryl groups such as **27** instead of their *ortho*- and *para*-substituted analogues; the absolute asymmetric photocyclization of the *m*-chloro-substituted oxoamide **27** resulted in **28** with 100% *ee*.[113]

Despite the fact that the benzyloxy moiety is rather remote the photocyclization led to β-lactams with high *ee* values. The



27 28

Scheme 12. Effect of *meta*-substituent X on the enantioselectivity of an absolute asymmetric cyclization of different 2-pyridones.[113]

remarkable enantioselectivity is attributed to intermolecular interactions in the solid state that discriminate between the two possible electrocyclization pathways. If the observations that *meta*-substituted arenes prefer to crystallize in non-centrosymmetric space groups, in comparison to the *ortho*- and *para*-isomers, have some generality[114, 115] then *meta*-substitution in an achiral compound could be an important structural motif in the design of new absolute asymmetric synthesis and to make it more predictable.

It should be emphasized that an achiral compound can show polymorphism. In the case of bis(biphenylmethylene)-*N*-methylsuccinimide only the solid-state photocyclization of the chiral form, in which the molecule adopts a helical conformation, provides optically active (*ee* = 64%) product.[116]

Absolute asymmetric synthesis using the chiral crystal field has also been demonstrated for other cycloadditions and photoreactions such as Norrish Type II photocyclization and di-π-methane-type photorearrangements.[117–119] The use of chiral bimolecular crystals,[120] chiral bimolecular charge-transfer complexes, and specific reactions on one face of an achiral crystal have also been demonstrated for absolute asymmetric synthesis.[121, 122]

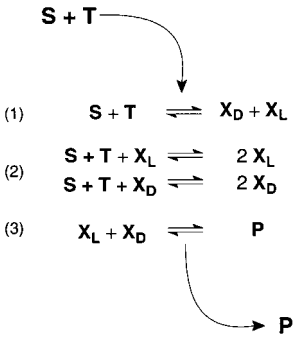
7. Amplification of Chirality

7.1. Autocatalysis and Nonlinear Effects

With the notable exception of asymmetric synthesis in enantiomorphic crystals and a few cases of CPL reactions the observed enantiomeric excesses in absolute asymmetric synthesis are extremely small. This means that an amplification mechanism is absolutely essential to enhance the initial chiral bias.

Also in light of the origin of biomolecular chirality, it is clear that observable consequences of the difference in the parity violating energy between enantiomeric molecules require some amplification mechanism. One possible method of amplification, based on a model for spontaneous symmetry breaking by Frank, is an autocatalytic system with competitive reactions of two enantiomers that are mutually inhibitory and form inactive products in a dynamic metastable system that is sensitive to small perturbations.[123] The reaction of two achiral compounds leads to two enantiomeric products that each catalyze their own formation, namely autocatalysis occurs. Simultaneously, each enantiomer reduces the activity of the other (mutual inhibition) resulting in a strong asymmetric amplification. Calculations on such a model system that is thermodynamically far from equilibrium show that this system can evolve spontaneously into a chirally asymmetric state.[124] In Scheme 13 a mechanism is depicted in which two enantiomeric forms of **X** ($\mathbf{X_L}$ and $\mathbf{X_D}$) are produced from achiral substrates (**S** and **T**) directly through Reaction (1) and autocatalytically through Reaction (2). By irreversible removal of the products (**P**) by Reaction (3) the system can be driven far from thermodynamic equilibrium.

A detailed study of the reaction rates show that the balance between autocatalysis and mutual annihilation is unstable,



Scheme 13. Chemical model system for the synthesis of chiral compounds from achiral precursors.[124]

with $\lambda = [\mathbf{S}]\,[\mathbf{T}]$ being the critical parameter. When λ is increased past a critical value (λ_c) the system will switch to a state where $\mathbf{X_L}$ ($\alpha = [\mathbf{X_L}] - [\mathbf{X_D}] > 0$) or $\mathbf{X_D}$ ($\alpha < 0$) is favored. The state that is reached without any chiral bias is of course completely random (such as in the case of the spontaneous asymmetric crystallization described above) but spontaneous symmetry breaking indeed occurs as was shown by computational simulation (Figure 8).[124] When the situation was biased, for instance by giving a slight preference for $\mathbf{X_L}$ over $\mathbf{X_D}$ (analogous to the possible effect of the Z force), the system almost always followed the branch where $\mathbf{X_L}$ dominated (Figure 8, right). It was predicted that in such a system

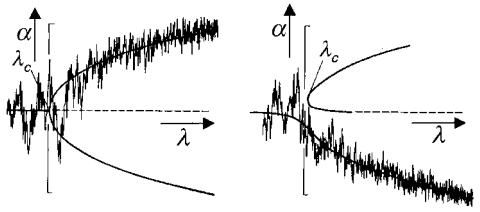
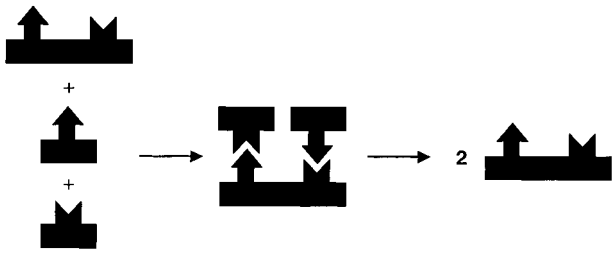


Figure 8. Evolution of chiral asymmetry (α) with time, without chiral bias (left) and with chiral bias (right). (From reference [124].)

the weak nuclear force should be capable, over a period of 50 000 – 100 000 years, to create a situation with at least a 98 % chance that nearly all molecules will be left-handed, as observed for terrestrial amino acids. This kind of system could provide a possible explanation for the origin of biomolecular asymmetry although it will not be easy to obtain experimental proof.

Self-replication and autocatalysis are among the most fascinating areas in chemistry today. In a self-replicating system, a molecule should function as a template for components that are bound by noncovalent interactions and are organized in such a way that they can react to form a copy of the original template molecule. In this way an autocatalytic synthesis is accomplished (Scheme 14). Following the pioneering work of the group of Orgel, who demonstrated the template-directed synthesis of complementary oligonucleotides,[125] von Kiedrowski reported the first example of a nonenzymatic self-replicating system that is based on the autocatalytic formation of a self-complementary hexanucleotide **29** (Figure 9).[126] The square root law of autocatalysis[127] was obeyed, as shown by the observed rate of the autocatalytic reaction being proportional to the square root of the concentration of the template.



Scheme 14. Schematic representation of autocatalysis.

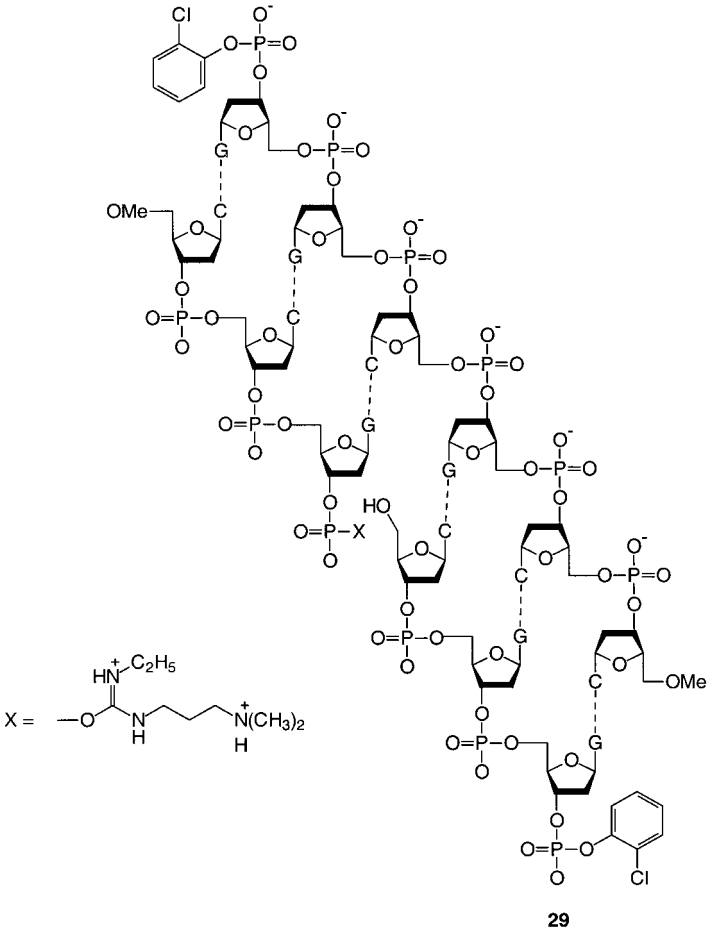


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Figure 9. Nonenzymatic self-replication.[126]

As a result of the efforts of the groups of Orgel, Rebek, von Kiedrowski, Nicolaou, and others a number of genuine self-replicating and autocatalytic systems are known today.[128] Figure 10 shows two synthetic models (**30** and **31**) that function as artificial self-replicators.[129, 130] Recently, Ghadiri et al. reported the first example of a self-replicating peptide.[131] A α-helical 32mer peptide with a sequence that is similar to the leucine-zipper domain of the yeast transcription factor GCN4 acts as a template for its own autocatalytic formation by coupling 15- and 17-oligopeptide residues.

In light of the discovery of enriched amino acids from extraterrestrial source (Section 2.2) and the stereoselection in oligopeptide formation (Section 7.2), the proposal that self-replicating peptide sequences should be considered in the early evolution of living systems is intriguing.

Asymmetric autocatalysis and nonlinear effects provide two mechanisms that can lead to amplification of chirality. A few early reports on the effect of chiral products on the stereochemical course of organometallic reactions and the

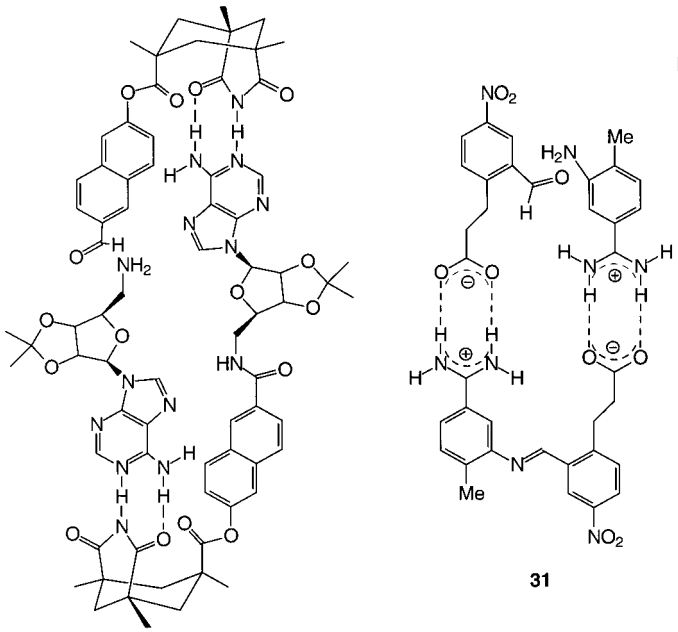
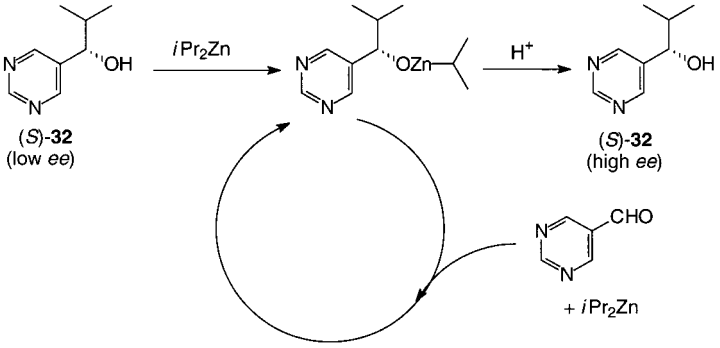


Figure 10. Synthetic models that function as artificial self-replicating systems.

observation of enantioselective autoinduction should be mentioned in this context.[132] A decade ago Wynberg advocated asymmetric autocatalysis as the major challenge in future asymmetric synthesis.[133] In 1990 Soai et al. found that the optically active pyridyl alcohol formed from pyridine-3-carbaldehyde and isopropylzinc is a chiral catalyst for its own formation.[134] Up until that time all systems resulted in a decrease of the *ee* value of the product. Soon after this first example of asymmetric autocatalysis, Danda et al. reported a strong asymmetric amplification of an optically active product by a co-catalytic effect in an addition of HCN to 3-phenoxybenzaldehyde catalyzed by a cyclic dipeptide.[135] This is an intriguing case of an asymmetric synthesis where the chiral product affects the chiral catalyst for the reaction and results in a strongly improved catalyst while simultaneously governing the absolute stereocontrol of its own formation.

A major breakthrough in this field was the finding by Soai et al. of catalytic asymmetric automultiplication in the addition of the dialkylzinc reagents to pyrimidine aldehydes without a decrease in the optical purity of the product.[136] These discoveries formed the basis for the first autocatalytic system that showed asymmetric amplification (Scheme 15).[137] The 1,2-addition in the presence of (*S*)-**32** with 2% *ee* gave additional (*S*)-**32** with 10% *ee* and further cycles enhanced the *ee* value to 88% with over a 900-fold increase in product formation. This represents an asymmetric autocatalytic amplification system in accordance with Frank's model. Recently, Soai et al. reported a similar autocatalytic reaction of pyrimidyl aldehydes using slightly enriched amino acids as the only chiral bias.[138] By this approach an *ee* value of up to 51% could be obtained. Interestingly from the point of view of the origin of chirality is the fact that the initial *ee* value of the amino acids used was equal to the *ee* value that could be obtained from asymmetric photolysis, as discussed above.[87]



Scheme 15. Proposed reaction scheme of asymmetric catalysis of **32** with enhancement of enantiomeric excess.

Highly relevant for amplification of the enantiomeric excess of the product of an absolute asymmetric synthesis is the so-called "nonlinear effect". Horeau found a strong deviation between optical purity, as determined by specific optical rotation, and the actual *ee* value of chiral succinic acids.[139] The nonlinear effect was attributed to diastereomeric association through hydrogen-bond formation. In 1976 Wynberg and Feringa discovered the so-called antipodal effects.[140] For instance, the diastereoselectivity in the $LiAlH_4$ reductions of camphor were found to depend on the *ee* value of the starting material, which pointed to a nonlinear effect in stoichiometric asymmetric synthesis. In 1986 Kagan was the first to observe significant nonlinear effects in three catalytic asymmetric reactions, namely asymmetric sulfoxidation, Sharpless epoxidation, and (*S*)-proline-catalyzed aldol cyclization.[141] Since then a variety of catalytic enantioselective reactions have been reported that show nonlinear behavior.[142] Kagan and Girard have extensively discussed the principles and important observations regarding nonlinear effects and we will focus only on the essential aspects of amplification.[143]

A linear relationship in an asymmetric catalytic reaction implies that the *ee* value of the product is proportional to the *ee* value of the chiral auxiliary, for instance a chiral ligand. The linear relationship is shown in Figure 11 and is given by Equation (2) for $g = 1$.[144]

$$ee_{\text{product}} = \left(ee_0 \frac{1 + \beta}{1 + g\beta}\right) ee_{\text{aux}} \qquad (2)$$

If diastereomeric associations between chiral species occur in nonhomochiral systems, deviation from the linear relationship [Eq. (2)] can occur leading to a positive nonlinear effect ($g < 1$; curve B in Figure 11) or a negative nonlinear effect ($g > 1$; curve C in Figure 11). For instance, the use of (−)-DAIB **33** as a chiral ligand in the ligand-accelerated catalytic addition of diethylzinc to benzaldehyde (Scheme 16), reported by Noyori et al., results in a dramatic nonlinear effect as is evident from Figure 12.[145] The asymmetric 1,2-addition of organozinc reagents has been studied in depth and the strong amplification is attributed to the formation of a stable (and therefore ineffective) heterochiral dimer **35** of the Zn-complex of the chiral ligand (Scheme 16).

Several models have been proposed to explain nonlinear effects in asymmetric catalysis.[143, 145–148] One model that

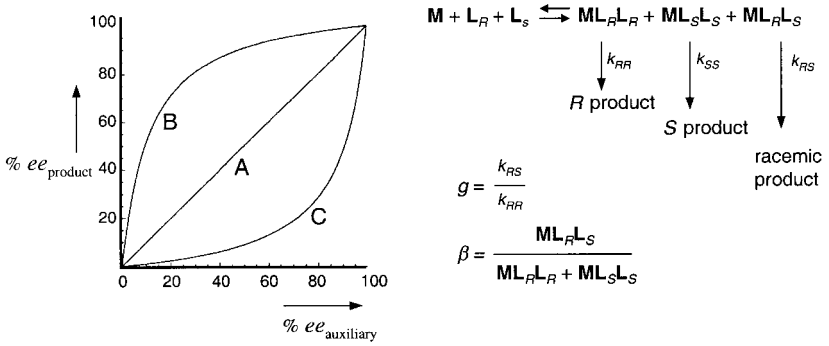
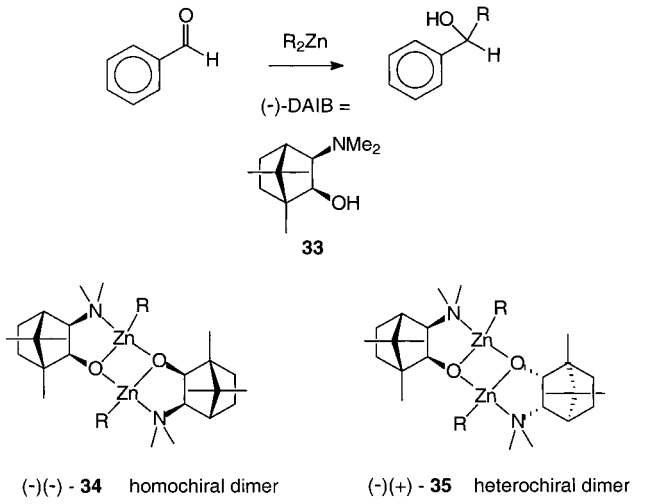


Figure 11. A) Linear relationship between the *ee* value of the chiral auxiliary and *ee* value of the product; B) positive nonlinear effect; C) negative nonlinear effect. (From reference [143].)

catalytically active species by the formation of inactive complexes that lead to an enhancement of the initial *ee* value of the chiral ligand. Optically active products will be produced by the homochiral catalyst while the *meso*-catalyst will lead to racemic product. Similar analyses apply for other metal–ligand combinations and non-metal-based chiral catalysts.

Nonlinear effects are a prominent feature of many catalytic asymmetric reactions and the self-amplification in the autocatalytic system reported by Soai et al. can be explained accordingly.



Scheme 16. (−)-DAIB-catalyzed addition of dialkylzinc to benzaldehyde. (From reference [145].)

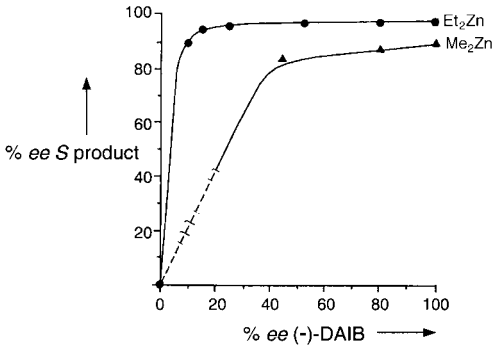
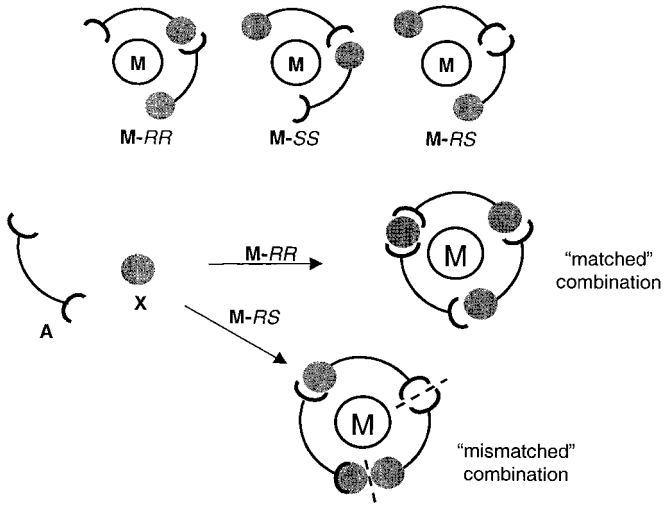


Figure 12. Observed nonlinear effects for the diethylzinc and dimethylzinc additions to benzaldehyde using (−)-DAIB as a catalyst. (From reference [145].)

provides a rational for asymmetric amplification is a catalyst model proposed by Bailey for a simple autocatalytic self-replicating system.[149] It comprises a metal complex, with two product molecules as the chiral ligand, that can only efficiently catalyze the formation of chiral product through the "matched" homochiral ligand combination (Scheme 17).

An amplification can be expected in two cases when a nonlinear effect is operating (Figure 11):[143] a) when the *meso*-catalyst is less reactive than the homochiral catalyst; b) when part of the chiral ligand is removed from the



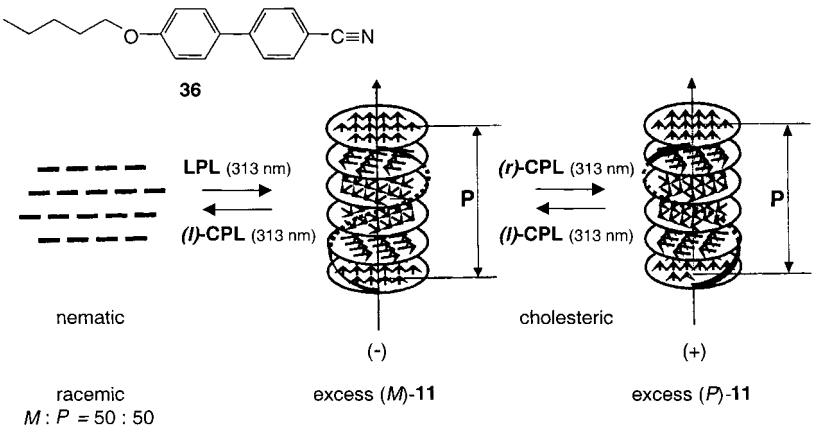
Scheme 17. Mechanisms for the asymmetric amplification in metal–ligand autocatalytic system (from reference [149]).

7.2. Amplification in Macromolecules and Supramolecular Assemblies

A delicate balance of noncovalent interactions, stereochemical features, and conformational flexibility is usually inherent in the successful assembly of large supramolecular structures.[150] This notion also implies that some of these systems are highly sensitive to chiral perturbations, in particular this is the case for liquid crystalline materials. It is well established that small amounts of an optically active guest molecule added to a nematic host could induce a cholesteric phase and that the helical organization in the mesoscopic system is very sensitive to modifications in the chiral guest molecule. The development of a switching and amplification system in which light can transform a nematic (achiral) liquid crystalline phase to a cholesteric (chiral) phase is appealing,[151] and in particular of interest for new information storage and display systems.[152]

The control and modulation of the chirality of the liquid crystalline mesophase was studied in our laboratory with the chiroptical molecular switch (Scheme 6).[96] Doping of the mesogen 4′-(pentyloxy)-4-biphenylcarbonitrile (**36**) with (*P*,*M*)-**11** (about 20 wt %) established a nematic phase, which upon irradiation at 313 nm with (*l*)- or (*r*)-CPL was converted

into a cholesteric phase. The photoresolution of guest **11** in the nematic host results in a small (0.07 %) *ee* value and, as a consequence a small helical twisting power and large pitch are observed. Furthermore, irradiation of the cholesteric phase containing excess (*M*)-**11**, obtained after CPL irradiation, with linearly polarized light (LPL) at 313 nm resulted in a nematic phase as a consequence of the formation of a 50:50 ratio of *P* and *M* helices of **11**, namely photoracemization occurs. The photochemical switching processes of the liquid crystalline phases are completely controlled by the changes in the chirality of the light at a single wavelength. The changes in liquid crystalline phases and dopant are shown in Scheme 18. Switching between LPL and CPL results in a nematic to

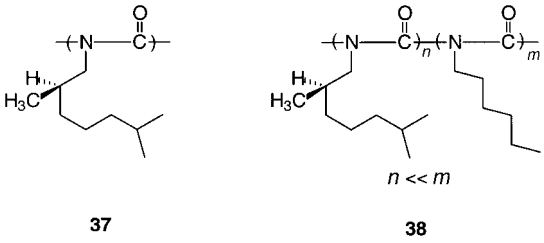


Scheme 18. Switching between three different liquid crystalline states after irradiation at one wavelength. For further information see the text.

cholesteric modulation. Switching between (*l*)-CPL and (*r*)-CPL modulates the chirality of the cholesteric phase (that is left- and right-handed, respectively). The low efficiency and the rather high dopant concentrations that are required in the current system need further improvement through structural modification of the photoresponsive guest molecule. It is fascinating to establish for the first time that an extremely small bias for a particular molecular chirality sense, induced by CPL photoresolution, can cause a major effect on the chiral organization of large ensembles of molecules and that this control of chirality is fully reversible.

Another possible mechanism for the amplification of an initial small enantiomeric excess in L-amino acids was proposed in which amplification occurs during the polymerization to proteins. A small difference in the activation parameters of enantiomeric monomers, effective at each stage of the polymerization, or an enhancement of the formation of an α-helical secondary protein structure by the employment of a single configuration of the amino acid can result in a relatively large enantiomeric excess of one of the homochiral polymers.[153] It was shown experimentally that the helical structure of poly(benzyl-L-glutamate) was progressively weakened when configuration randomness was introduced by substitution of L-glutamate units by their D-enantiomers.[154] Polymerization of leucine with 31.1 % *ee* (L > D) gave polyleucine with 45.4 % *ee*.[155] When this polyleucine of 45.4 % *ee* is subsequently partially hydrolyzed the residual monomer shows a lower *ee* value of 30.5 to 43.7 %, while the residual unhydrolyzed polymer shows an enhancement of 49.5 to 54.9 % *ee*.[156] According to these results a repeated cycle of polymerization and hydrolysis could be an efficient method of enhancing an initial small enantiomeric bias. It was suggested that environmental dry/wet cycles on the primitive Earth might have caused repeated polymerization/hydrolysis cycles that permitted the eventual evolution of optical purity from a small abiotic *ee* value in amino acids.[155]

Cooperative responses to chiral information and magnification effects can also be extremely large in helical polymers.[157] Pioneering studies show that polyalkylisocyanates such as polyhexylisocyanate form left- and right-handed helices although the monomers themselves are achiral.[158] Green et al. demonstrated that helical reversals along the chain are highly sensitive to chiral effects. Incorporation of a small number of units with pendant chiral groups, for example **37**, in co-polymers with hexylisocyanate, results in the control of helical reversals that forces large numbers of polymer chain units to cooperate in directing the chirality of the polymer. On the basis of these findings Green et al. formulated a majority rule and the so-called "sergeants and soldiers" principle. A tiny majority of *R* over *S* monomers or a small amount of chiral units (sergeants) incorporated within the achiral units (soldiers), for example, hexylisocyanate units in polymer **38**, can dictate the helical sense (Figure 13). This powerful amplification mechanism is highly attractive for the magnification of the small chiral bias that is reached with CPL photoresolution.

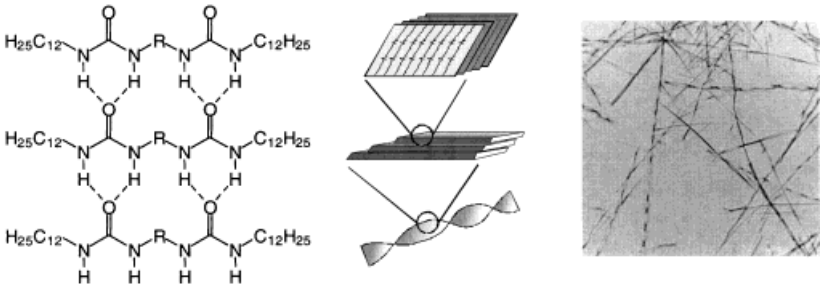


37 38

Figure 13. Optically active polyisocyanates.

Recently, an approach that incorporates a photoresponsive racemic unit into a polyisocyanate and uses CPL resolution of such a trigger element to control the helical sense of the polymer (and to amplify the chiral bias) has been successful.[159] These types of amplification mechanisms will attract considerable interest in the coming years as similar effects have been observed in other helical polymers[160] and dynamic aggregates of disc-shaped molecules.[161]

Finally, it should be emphasized that chirality at a molecular level is not a prerequisite to observe chirality at the macroscopic level, that is, it is not essential to have chiral molecules as building blocks. An illustrative example is shown in Figure 14. Achiral bisurea compounds (low molecular weight



39

Figure 14. Chiral aggregates formed from achiral bisurea building blocks.

gelators, for example, **39**) undergo efficient and spontaneous self-assembly to form micrometer-long fibers with strong helical twisting.[162] Apparently, strong anisotropic growth and small distortions cause the macroscopic helicity. Clearly, there is no stereochemical bias as both left- and right-handed helices are formed.

8. Summary and Outlook

There are few areas in chemistry that have experienced the pace of progress seen in asymmetric synthesis in the last decade. It is remarkable that since the early days of organic stereochemistry in the last century the challenge and excitement to perform absolute asymmetric synthesis was felt. Despite the numerous attempts and some remarkable achievements, in particular using circularly polarized light for photochemical conversions and with solid-state reactions in the last few years, the challenge remains as strong as ever. It is doubtful if absolute asymmetric synthesis will be of much use to our synthetic repertoire for the preparation of homochiral compounds. More important is the experimental proof of absolute asymmetric synthesis in the context of the origin of biomolecular chirality and the ways chiral information can be transferred from a molecular level to supra- and macromolecular levels. New discoveries that might point to a potential extraterrestrial origin of chirality and theoretical models for the spontaneous resolution and symmetry breaking are highly intriguing in this respect.

Mechanisms associated with the amplification of chirality and autocatalytic and self-replicating systems are pertinent to this field. The amplification of a small stereochemical bias resulting from absolute asymmetric synthesis remains a major goal, although the first examples in which chiral amplification is demonstrated in autocatalytic and supramolecular systems, such as liquid crystalline materials, look highly promising.

Since absolute asymmetric synthesis and the origin of chirality are intimately related to asymmetric autocatalysis, self-replicating systems, and molecular amplification mechanisms several exciting discoveries are ahead of us—most probably on the trail of the origin of chemical evolution itself.

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[163] Note added in proof: a) After submission of this manuscript a study on the influence of parity-violating energy difference in the crystallization process of cobalt and iridium complexes appeared: A. Szabó-Nagy, L. Keszthelyi, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4252 – 4255. b) An example of spontaneous resolution in a fluid liquid crystalline phase: Y. Takanishi, H. Takezoe, Y. Suzuki, I. Kobayashi, T. Yajima, M. Terada, K. Mikami, *Angew. Chem.* **1999**, *111*, 2502 – 2504; *Angew. Chem. Int. Ed.* **1999**, *38*, 2354 – 2536 (see also references cited therein on 2-dimenisonal conglomerate formation).