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# Possible chemical and physical scenarios towards biological homochirality†

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The single chirality of biological molecules in terrestrial biology raises more questions than certitudes about its origin. The emergence of biological homochirality (BH) and its connection with the appearance of life have elicited a large number of theories related to the generation, amplification and preservation of a chiral bias in molecules of life under prebiotically relevant conditions. However, a global scenario is still lacking. Here, the possibility of inducing a significant chiral bias "from scratch", *i.e.* in the absence of pre-existing enantiomerically-enriched chemical species, will be considered first. It includes phenomena that are inherent to the nature of matter itself, such as the infinitesimal energy difference between enantiomers as a result of violation of parity in certain fundamental interactions, and physicochemical processes related to interactions between chiral organic molecules and physical fields, polarized particles, polarized spins and chiral surfaces. The spontaneous emergence of chirality in the absence of detectable chiral physical and chemical sources has recently undergone significant advances thanks to the deracemization of conglomerates through Viedma ripening and asymmetric auto-catalysis with the Soai reaction. All these phenomena are commonly discussed as plausible sources of asymmetry under prebiotic conditions and are potentially accountable for the primeval chiral bias in molecules of life. Then, several scenarios will be discussed that are aimed to reflect the different debates about the emergence of BH: extra-terrestrial or terrestrial origin (where?), nature of the mechanisms leading to the propagation and enhancement of the primeval chiral bias (how?) and temporal sequence between chemical homochirality, BH and life emergence (when?). Intense and ongoing theories regarding the emergence of optically pure molecules at different moments of the evolution process towards life, *i.e.* at the levels of building blocks of Life, of the instructed or functional polymers, or even later at the stage of more elaborated chemical systems, will be critically discussed. The underlying principles and the experimental evidence will be commented for each scenario with particular attention on those leading to the induction and enhancement of enantiomeric excesses in proteinogenic amino acids, natural sugars, and their intermediates or derivatives. The aim of this review is to propose an updated and timely synopsis in order to stimulate new efforts in this interdisciplinary field.

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## 1. Introduction

In 1884, Lord Kelvin used the word chirality—derived from the Proto-Indo-European *ǵʰesr through the Ancient Greek χειρ (kheír), which both mean 'hand'—and gave the following definition: "an object is chiral if and only if it is not superimposable on its mirror image".[1] Additionally, chirality can be described based on symmetry aspects: an object is chiral if it possesses no symmetry elements of the second kind (*i.e.* if it is devoid of any improper axis of rotation).[2] Whilst the manifestation of chirality at the macroscopic scale sparked human's curiosity from antiquity, its observation at the molecular and sub-atomic levels is relatively recent. In the 19th-century, advances made in optics,[3] crystallography[4] and chemistry[5] paved the way to the scientific study of molecular chirality (named 'molecular dissymmetry' by Louis Pasteur)[6] which soon after manifested itself in a variety of studied phenomena. The term "chirality" took additionally almost 80 years to be introduced in chemistry by Kurt Mislow (1962).[7]

Chirality is found at all scales in matter, from elementary particles to cucumber tendrils,[8] from screws to spiral galaxies, in living and inert systems.[9] It is also an everyday concern in industry (*e.g.* pharma, agribusiness, and cosmetics)[10–14] as well

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† Dedicated to the memory of Sandra Pizzarello (1933–2021).

as in fundamental research (visible in countless conferences encompassing not only chemistry, physics, and biology but also economy and arts).[15]

Homochirality of life refers to the fact that Nature has chosen a specific handedness. Homochirality is a fascinating aspect of terrestrial biology: all living systems are composed of L-amino acids and D-sugars‡ to such an elevated extent that the occurrence of the molecules of life with different configurations (*e.g.* D-amino acids) is seen as a curiosity.[16] Clearly, the perfect level of selectivity reached by evolution and preserved along billion years, is out of reach for currently developed artificial systems. Homochirality and life are so closely related that homochirality in Nature is considered as a stereochemical imperative.[17] For example, D-sugars are building blocks of helically shaped DNA and RNA macromolecules, which store genetic information and encode the synthesis of proteins through the ligation of their constituting amino acids. Glucose

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‡ Proteinogenic amino acids and natural sugars are usually mentioned as L-amino acids and D-sugars according to the descriptors introduced by Emil Fischer. It is worth noting that natural L-cysteine (*R*) uses the Cahn–Ingold–Prelog system, due to the sulfur atom in the side chain which changes the priority sequence. In the present review, (*R*)/(*S*) and D/L descriptors will be used for amino acids and sugars, respectively, as commonly employed in the literature dealing with BH.

**Quentin Sallembien**

*Quentin Sallembien was born in 1993 in Strasbourg, France. He got an engineering diploma from ENSCBP – Bordeaux INP (2017) and obtained in 2021 a doctoral degree under the supervision of Dr Matthieu Raynal (Sorbonne Université). His PhD research focused on controlling the handedness of supramolecular helical polymers by means of circularly polarized light and chiral additives. He is currently a postdoctoral researcher in the group of Prof. Renaud Nicolaÿ at ESPCI Paris, dealing with polyolefin vitrimers.*

**Laurent Bouteiller**

*Laurent Bouteiller is the CNRS Research Director and head of the Polymer Chemistry lab at Sorbonne Université in Paris. His main research interests are focused on the interface between polymer science and supramolecular chemistry, which involves using non-covalent interactions to assemble molecules. The low energies involved make it possible to control the formation of complex architectures and to obtain materials with reversible properties of interest in various fields (e.g. rheology, catalysis, adhesion, and coatings).*

**Jeanne Crassous**

*Dr Jeanne Crassous (born Costante) received her PhD in 1996 under the supervision of Prof. André collet (ENS, Lyon, France), working on the absolute configuration of bromochlorofluoromethane. After a one-year postdoctoral period studying the chirality of fullerenes in Prof. François Diederich's group (ETH Zurich, Switzerland), she was appointed a CNRS researcher at the ENS Lyon in 1998. In 2005, she joined the "Institut des Sciences Chimiques de Rennes" (University of Rennes, France) and was appointed a CNRS Director of Research in 2010. Her group works on many fields related to chirality (organometallic and heteroatomic helicenes, fundamental aspects of chirality such as parity violation effects, chiroptical activity such as electronic and vibrational circular dichroism and circularly polarized luminescence). In 2020, she received the National Prize of the Organic Chemistry Division of the French Chemical Society (DCO-SCF).*

**Matthieu Raynal**

*Matthieu Raynal got his PhD degree under the supervision of Dr P. Braunstein in 2009 (Strasbourg). He conducted postdoctoral studies at UPMC with L. Bouteiller (Paris) and in the group of Prof. P. W. N. M. van Leeuwen at ICIQ (Tarragona, Spain). In 2012, he was appointed as a CNRS researcher at Sorbonne Université, Paris. He is fascinated by how non-covalent interactions can be designed to control the outcome of a catalytic reaction, i.e. supramolecular catalysis. His group is currently developing supramolecular helical catalysts with particular efforts devoted to improving their chirality amplification and switchable properties. His research activities also concern the design of functional chiral assemblies and the structure–property relationship of supramolecular polymers. He recently co-edited with P. W. N. M. van Leeuwen the book "Supramolecular Catalysis: New Directions and Developments" (2022 Wiley-VCH GmbH).*

monomers in glycogen, starch and cellulose also have a D configuration. This suggests that the chirality, structure, and functions of these biomacromolecules are intimately related.[18]

In 1857, Louis Pasteur revealed the dramatic difference in the fermentation rate of two tartaric acid enantiomers with a yeast microorganism, thus uncovering biological enantioselectivity.[19–21] Pasteur was convinced that chirality was a manifestation of life, and unsuccessfully looked for the link between physical forces ruling out the Cosmos and the molecular dissymmetry observed in natural products. In 1886, an Italian chemist Arnaldo Piutti[22] succeeded in isolating (*R*)-asparagine, mirror-image of the tasteless amino-acid (*S*)-asparagine, and found that it was intensely sweet.[23] These discoveries refer to the link between the handedness of chiral substances and their biological properties but do not explain the origin of biological homochirality (BH).

Despite the extensive literature, the emergence of BH remains a conundrum.[24–44] The key points of this intricate topic can be summarized as: how, when and where did single chirality appear and eventually lead to the emergence of life (Fig. 1).[45–48] Along this line, the question of the creation of the original chiral bias appears critical (box ''how?'' in Fig. 1). Huge efforts have been dedicated to decipher which processes may lead to the generation of a chiral bias without the action of pre-existing enantiomerically enriched chemical species, that is without using the commonly employed routes in stereoselective synthesis. The creation of a chiral bias ''from scratch'', often referred to as absolute asymmetric synthesis[30,31,49,50] and spontaneous deracemization,[41,51,52] actually encompasses a large variety of phenomena. Here, a distinction can be made between chiral biases that: (i) are inherent to the nature of matter itself, (ii) originate from the interaction of molecules with physical fields, particles, spins or surfaces, or (iii) emerge from the mutual interaction between molecules (Fig. 1). The first category (i) corresponds to the fact that a racemate deviates infinitesimally from its ideal equimolar composition deterministically, *i.e.* in direction of the same enantiomer for a given racemate, as a result of parity violation in certain interactions within nuclei.[53,54] The second category (ii) refers to natural physical fields (gravitational, magnetic, and electric), light and their combinations, which under certain conditions constitute truly chiral fields,[30] but also to a range of inherently chiral sources such as chiral light and polarized particles (mostly electrons), polarized electron spins, vortices, or surfaces.[44] The third category (iii) encompasses processes that lead to the spontaneous emergence of chirality in the absence of detectable chiral physical and chemical sources, upon destabilization of the racemic state and stabilization of a scalemic or homochiral state. Such spontaneous mirror symmetry breaking (SMSB) phenomena[40] involve interactions between molecules through auto-catalytic processes which under far-from-equilibrium conditions may lead to the emergence of enantiopure molecules. The topic has recently undergone significant progress thanks to numerous theoretical models and experimental validations, namely the deracemization of conglomerates through Viedma ripening[55] and the asymmetric auto-catalysis with the Soai reaction.[56] Importantly, the plausibility of the aforementioned chirality induction processes in the context of BH will depend on several parameters such as: the extent of asymmetric induction they may provide, their mode of action, *i.e.* if they are unidirectional (deterministic towards a single enantiomer) or bidirectional (leading to either type of enantiomers), their relevance according to prebiotic conditions present on earth 4 billion years ago, the scope of molecules it could be applied to, and their validation by experimental evidence. The first three parts of this review will provide an updated version of phenomena i–iii that are commonly discussed as plausible sources of asymmetry under prebiotic conditions and can thus be potentially accountable for the primeval chiral bias in molecules of life.

However, uncovering plausible mechanisms towards the emergence of a chiral bias is not enough *per se* for elucidating

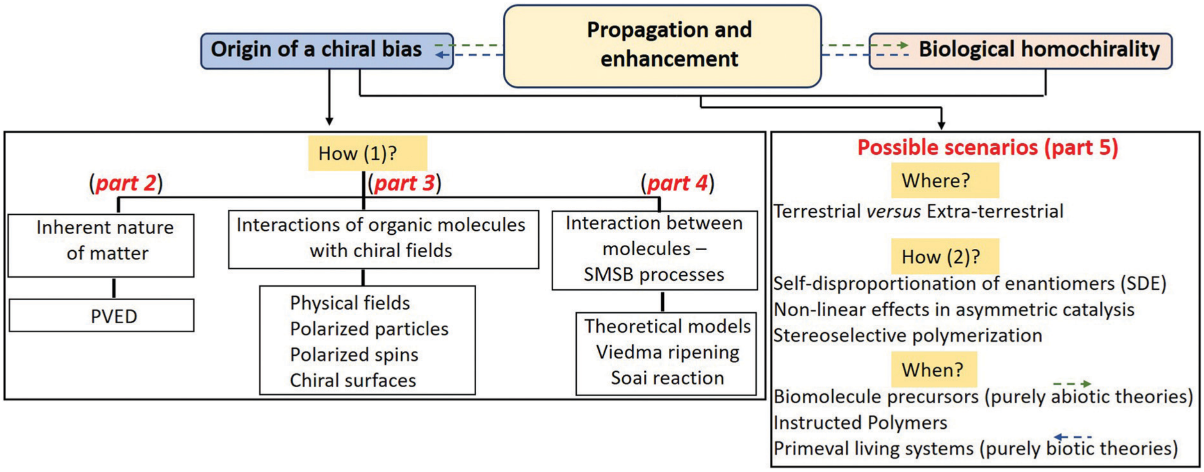

Fig. 1 Schematic representation of the questions and potential answers which are fundamentally related to the conundrum of the origin of the homochirality of life. This review is divided into 4 parts as indicated in the scheme. PVED: parity-violating energy difference. SMSB: spontaneous mirror symmetry breaking.

the origin of BH. Additional fundamental challenges such as the extra-terrestrial or terrestrial origin of molecule of life precursors (box ''where?'' in Fig. 1), the mechanism(s) for the propagation and enhancement of the original chiral bias (box ''how 2?'' in Fig. 1) and the chemical/biological pathways leading to functional bio-relevant molecules are key aspects to propose a credible scenario. The detection of amino acids and sugars with preferred L and D configurations, respectively, on carbonaceous meteorites[57] instigated further research for determining plausible mechanisms for the production of chiral molecules in an interstellar environment and their subsequent enantiomeric enrichment.[58,59] Alternatively, hydrothermal vents in primeval oceans constitute an example of reaction domains often evoked for prebiotic chemistry which may also include potential sources of asymmetry such as high-speed microvortices.[60] Some mechanisms are known for increasing an existing e.e., such as the self-disproportionation of enantiomers (SDE),[61] non-linear effects in asymmetric catalysis,[62,63] and stereoselective polymerization.[64] Noteworthy in the present context, these processes may be applied to increase the optical purity of prebiotically relevant molecules. However, a general amplification scheme which is valid for all molecules of life is lacking.

The temporal sequence between chemical homochirality, BH and life emergence is another intricate point (box ''when?'' in Fig. 1). Tentative explanations try to build-up either abiotic theories considering that single chirality is created before the living systems or biotic theories suggesting that life preceded homochirality.[44] Purely abiotic theories refer to reactions or physicochemical processes involving low-molecular weight organic molecules presumably present in the prebiotic soup.[38,65] From a different angle, polymerization of activated building blocks is also discussed as a possible stage for the induction/enhancement of chirality,[64] even though prebiotic mechanisms towards these essential-to-life macromolecules remain highly elusive.[45–48] In the fifth part of this review, we will propose an update of the most plausible chemical and physical scenarios towards BH, with emphasis on the underlying principles and the experimental evidence, showing merits and limitations of each mechanism. Notably, relevant experimental investigations conducted with building blocks of life: proteinogenic amino acids, natural sugars, and their intermediates or derivatives, will be commented in regards of the different scenarios.

Ultimately, the aim of this literature review is to familiarize the novice with research dealing with BH, and to propose to the expert an updated and timely synopsis of this interdisciplinary field.

## 2. Parity violation (PV) and parity-violating energy difference (PVED)

''Videmus nunc per speculum in aenigmate,'' (Holy Bible, I Cor. XIII, 12) which can be translated into ''At present, we see indistinctly, as in a mirror'' refers to the intuition that a mirror reflection is a distorted representation of the reality. The perception of a different nature of mirror-image objects is also found in the modern literature. In his famous novel ''Through the Looking-Glass'' by Lewis Caroll Alice raises important questions: 'How would you like to live in Looking-glass House, Kitty? I wonder if they'd give you milk in there? Perhaps Looking-glass milk isn't good to drink...''

The Universe is constituted of elementary particles which interact through fundamental forces, namely the electromagnetic, strong, weak, and gravitational forces. Until the mid-20th century, fundamental interactions were thought to equally operate in a physical system and its image built through space inversion. Indeed, these laws were assumed by physicists to be conserved under the parity operator $P$ (which transforms the spatial coordinates $x$, $y$, $z$ into $-x$, $-y$, $-z$), *i.e.* parity-even. However, in 1956, Lee and Yang highlighted that parity was only conserved for strong and electromagnetic forces, and proposed experiments to test it for weak interactions.[66] A few months later, Wu experimentally demonstrated that the parity symmetry is indeed broken in weak forces (which are hereby parity-odd),[67] by showing that the transformation of unstable $^{60}$Co nuclei into $^{60}$Ni, through the $\beta^-$-decay of a neutron into a proton, emits electrons of only left-handedness. In fact, solely left-handed electrons were emitted since $W^+$ and $W^-$ bosons (abbreviated as $W^{\pm}$ bosons), which mediate the weak charged-current interactions, only couple with left-handed particles. Right-handed particles are not affected by weak interactions carried out by $W^{\pm}$ bosons and consequently, neutrinos, that are only generated by processes mediated by $W^{\pm}$ bosons, are all left-handed in the universe.[68]

The weak neutral current interactions, mediated by the $Z^0$ boson (sometimes called Z forces), are without charge exchange and, just like the charged ones, violate the parity symmetry.[69–73] Thus, all weak interactions, carried out by $W^{\pm}$ or $Z^0$ bosons, break the fundamental parity symmetry.

Parity violation has been observed in nuclear[67] and atomic Physics.[74–77] In consequence, the contribution of the Z force between the nuclei and electrons produces an energy shift between the two enantiomers of a chiral molecule. The lower-energy enantiomer would thus be present in slight excess in an equilibrium mixture; this imbalance may provide a clue to the origin of biomolecular homochirality, *i.e.* why chiral molecules usually occur in a single enantiomeric form in nature. Such a tiny parity violation energy difference (a PVED of about $10^{-17}$ kT at 300 K) should be measurable by any absorption spectroscopy provided that ultra-high resolution can be reached.[78–81] Over the past decades, various experiments have been proposed to observe parity violation in chiral molecules, including measurements of PV frequency shifts in NMR spectroscopy,[82] measurements of time dependence of optical activity,[83] and direct measurement of the absolute PV energy shift of the electronic ground state.[79–81,84]

However, it has never been unequivocally observed at the molecular level to date. Note that symmetry violation of time reversal ($T$) and of charge parity (CP) is actually recovered in the CPT symmetry, *i.e.*, in the ''space-inverted anti-world made of antimatter".[85] Quantitative calculations of this parity-violating energy difference between enantiomers have been improved during the last four decades,[86–90] to give for example about $10^{-12}$ J mol$^{-1}$ for CHFClBr.[91,92] Although groups of Crassous/Darquié in France[78,93–98] and Quack in Switzerland[99–103] have been pursuing an experimental effort to measure PVED, thanks to approaches based on spectroscopic techniques and/or tunneling processes, no observation has unambiguously confirmed it yet. However, thanks to the combination of the contribution from the weak interaction Hamiltonian ($Z^3$) and from the spin orbit coupling ($Z^2$), the parity violating energy difference strongly increases with increasing nuclear charge with a commonly accepted $Z^5$ scaling law, thus chiral heavy metal complexes might be favourable candidates for future observation of PV effects in chiral molecules.[94,96] Other types of experiments have been proposed to measure PV effects, such as nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), microwave (MW) or Mössbauer spectroscopy.[79] Note that other phenomena have been taken into consideration to measure PVED such as in Bose–Einstein condensation, but those were not conclusive.[104,105]

The tempting idea that PVED could be the source of the tiny enantiomeric excess amplified to the asymmetry of life was put forward by Ulbricht in 1959[106,107] and by Yamagata in 1966.[108] With this in mind, Mason, Tranter and MacDermott[109–122] defended in the eighties and early nineties that (*S*)-amino acids, D-sugars, α-helix or β-sheet secondary structures, and other natural products and secondary structures of biological importance are more stable than their enantiomorph due to PVED.[54] However, Quack[89,123] and Schwerdtfeger[124,125] independently refuted these results on the strength of finer calculations, and Lente[126,127] asserted that a PVED of around $10^{-13}$ J mol$^{-1}$ causes an excess of only $6 \times 10^6$ molecules in one mole (against $1.9 \times 10^{11}$ for the standard deviation). In reply, MacDermott claimed, by means of a new generation of PVED computations, that the enantiomeric excess of four gaseous amino acids found in the Murchison meteorite (in the solid state) could originate from their PVED.[128,129] Whether PVED could have provided a sufficient bias for the emergence of BH likely depends on the related amplification mechanism, a point that will be discussed in more detail in part 4.

## 3. Chiral fields

Physical fields, polarized particles, polarized spins and surfaces are commonly discussed as potential chiral inducers of enantiomeric excesses in organic molecules. The aim of this part is to present selected chiral fields along with experimental observations which are relevant in the context of elucidating BH.

### 3.1 Physical fields

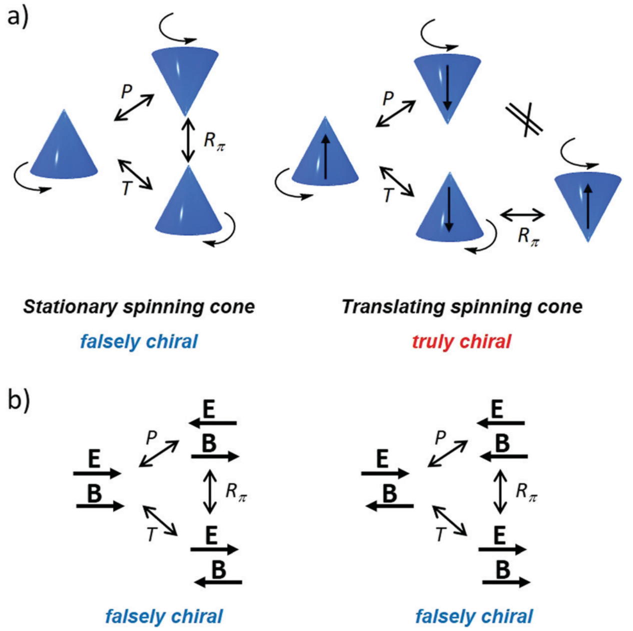

Fig. 2 Distinction between "true" and "false" chirality[30,130] by considering the effect of parity (*P*) and time (*T*) reversal on spinning cones (a) and aligned magnetic and electric fields (b).

**(a) True and false chirality.** Chirality's definitions based on symmetry arguments are adequate for stationary objects, but not when motion comes into play. To address the potential chiral discriminating nature of physical fields, Barron defined true and false chirality as follows: the "true chirality is shown by systems existing in two distinct enantiomeric states that are interconverted by space inversion (*P*), but not by time reversal (*T*) combined with any proper spatial rotation ($R_\pi$)".[130] Along this line, stationary and translating rotating cones are prototypical representations of false and true chirality, respectively (Fig. 2a). Cones help to better visualize the true chiral nature of vortices, but the concept is actually valid for any translating spinning objects, *e.g.* photons and electrons.[85,131] All experimental attempts to produce any chiral bias using a static uniform magnetic or electric field, or unpolarized light failed and this can be explained by the non-chiral nature of these fields.[30,31,49] In addition, the combination of static uniform magnetic and electric fields, whatever parallel or antiparallel, constitutes another example of false chirality (Fig. 2b).[30]

Importantly, only when interacting with a truly chiral system the energy of enantiomeric probes can be different (corresponding to diastereomeric situations), while no loss of degeneration in energy levels can happen in a falsely chiral system; however, asymmetry could be obtained for processes out of thermodynamic equilibrium.[30,31] Based on these definitions, truly chiral forces may lift the degeneracy of enantiomers and induce enantioselection in a reaction system reaching its stationary state, while an influence of false chirality is only possible for kinetically controlled reaction outputs, since in this case the enantiomers remain strictly degenerate and only the breakdown of the reaction path microreversibility occurs.[41] Furthermore, the extent of chiral induction that can be achieved by a chiral physical field is intimately related to the nature of its interaction with matter, *i.e.* with prebiotically relevant organic molecules in the context of BH. A few examples of physical fields for absolute asymmetric synthesis are mentioned in the next paragraphs.

**(b) Magnetochiral effects.** A light beam of arbitrary polarization (with k as the wavevector) propagating parallel to a static magnetic field (B) also possesses true chirality ($k{\cdot}B$), exploited by the magneto-chiral dichroism (MChD, Fig. 3a).[132] MChD was first observed by Rikken and Raupach in 1997 for a chiral europium(III) complex, and was further extended to other metal compounds and a few aggregates of organic molecules.[132–136] Photoresolution of $\Delta$- and $\Lambda$-chromium(III) tris(oxalato) complexes thanks to magnetochiral anisotropy was accomplished in 2000 by the same authors,[137] with an enantioenrichment proportional to the magnetic field, e.e./$B$ being equal to $1 \times 10^{-5}$ $T^{-1}$ (Fig. 4b).

**(c) Mechanical chiral interactions.** Whilst mechanical interactions of chiral objects with their environment is well established at the macroscale, the ability of these interactions to mediate the separation of molecular enantiomers remains largely under-explored.[139] A few experimental reports indicate that fluid flows can discriminate not only large chiral objects,[140–142] but also helical bacteria,[143] colloidal particles,[144] and supramolecular aggregates.[145,146] It has been indeed found that vortices, being induced by stirring, microfluidics or temperature gradients, are capable of controlling the handedness of supramolecular helical assemblies.[60,145–159] Laminar vortices have been recently employed as the single chiral discriminating source for the emergence of homochiral supramolecular gels in milliseconds.[60] High speed vortices have been evoked as potential sources of asymmetry present in hydrothermal vents, presumed key reaction sites for the generation of prebiotic molecules. However, the propensity of shear flow to prevent the Brownian motion and allow for the discrimination of small molecules remains to be demonstrated. Grzybowski and co-workers showed that *s*-shaped μm-sized particles located at the oil/air interface parallel to the shear plane migrate to different positions in a Couette cell.[160] The proposed chiral drift mechanism may in principle allow the separation of smaller chiral objects, with size in the order of tens of nanometres. In 2015, a new molecular parameter called hydrodynamic chirality was introduced to characterize the coupling of rotational motion of a chiral molecule to its translational motion and quantify the direction and velocity of such motion.[138]

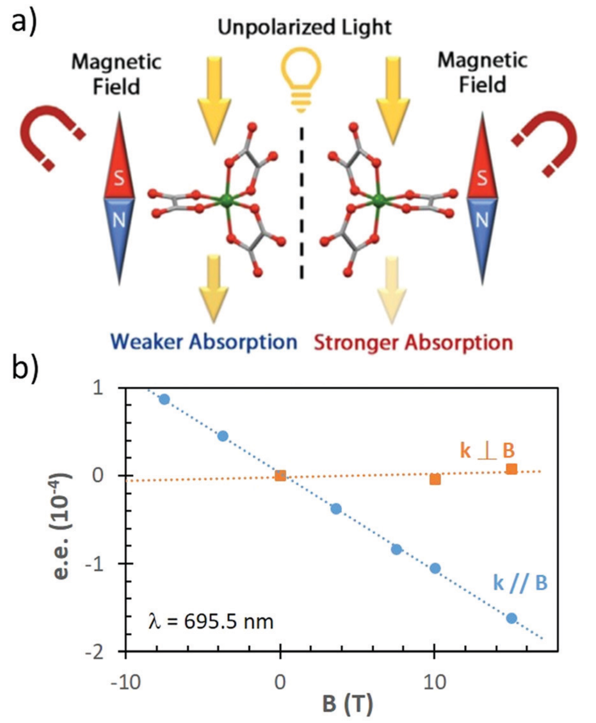

Fig. 3 (a) Schematic representation of MChD for a racemate of a metal complex: the unpolarised light is preferentially absorbed by $\Lambda$ *versus* $\Delta$ enantiomers. Reprinted from ref. 136 with permission from Wiley-VCH, copyright 2020. (b) Photoresolution of the chromium(III) tris(oxalato) complex. Plot of the e.e. after irradiation with unpolarised light for 25 min at $\lambda$ = 695.5 nm, as a function of the magnetic field, with an irradiation direction *k*, either parallel or perpendicular to the magnetic field.[137]

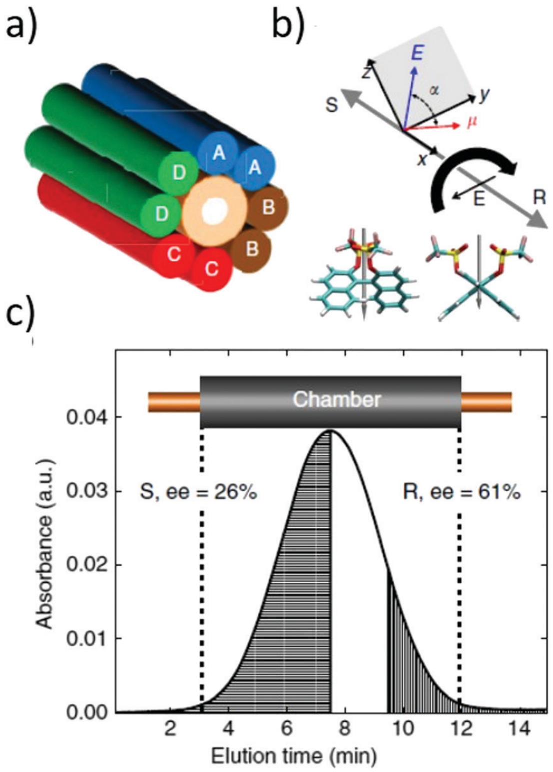

Fig. 4 (a) Schematic representation of the experimental set-up for the separation of chiral molecules placed in a microfluidic capillary surrounded by rotating electric fields (A–D electrodes). (b) Expected directions of motion of the enantiomers of 1,1′-bi-2-naphthol bis(trifluoromethanesulfonate) for the indicated direction of rotation of REF (curved black arrow). α is the relative angle between the electric dipole moment and electric field. The grey arrows show the opposite directions of motion of the enantiomers. (c) Absorbance chromatogram from the in-line detector of a slug of (*rac*)-1,1′-bi-2-naphthol bis(trifluoromethanesulfonate) after exposure to clockwise REF for 45 h. The sample collected from the shaded left side of the chromatogram had an e.e. of 26% in favour of the (*S*) enantiomer, while the right shaded section of the chromatogram had an e.e. of 61% for the (*R*) enantiomer. Reprinted ref. 138. Copyright 2015. Springer Nature under Creative Commons Attribution 4.0 International License https://creativecommons.org/licenses/by/4.0/.

The concept concerns the possibility to control the motion of chiral molecules by orienting and aligning their dipole moment with the electric field position leading to their rotation. The so-called molecular propeller effect allows enantiomers of two binaphthyl derivatives, upon exposition to rotating electric fields (REF), to propel in opposite directions, leading to a local enrichment of up to 60% e.e. (Fig. 4). It would be essential to probe the interactions of vortices, shear flows and rotating physical fields with biologically relevant molecules in order to uncover whether they could have played a role in the emergence of a chiral bias on early earth.

**(d) Combined action of gravity, magnetic field and rotation.** Micali *et al.* demonstrated in 2012 that the combination of gravity, magnetic field and rotation can be used to direct the handedness of supramolecular helices generated upon assembly of an achiral porphyrin monomer (TPPS$_3$, Fig. 5).[161] It was presumed that the enantiomeric excess generated at the onset of aggregation was amplified by the autocatalytic growth of the particles during the elongation step. The observed chirality is correlated to the relative orientation of the angular momentum and the effective gravity, the direction of the former being set by clockwise or anticlockwise rotation. The role of the magnetic field is fundamentally different than that in the MChD effect (Part 3.1(a)) since its direction does not influence the sign of the chiral bias. Its role is to provide tunable magnetic levitation force and alignment of the supramolecular assemblies. These results therefore seem to validate experimentally the prediction by Barron that false chiral influence may lead to absolute asymmetric synthesis after enhancement of an initial chiral bias created under far-from-equilibrium conditions.[130] According to the authors, control experiments performed in the absence of magnetic field discard the macroscopic hydrodynamic chiral flow, *i.e.* a true chiral force (see Part 3.1(c)), as the driving force for chirality induction; a point that has been recently disputed by other authors.[41] Regardless of the true of false nature of the combined action of gravity, magnetic field and rotation, its potential connection to BH is hard to conceive at this stage.

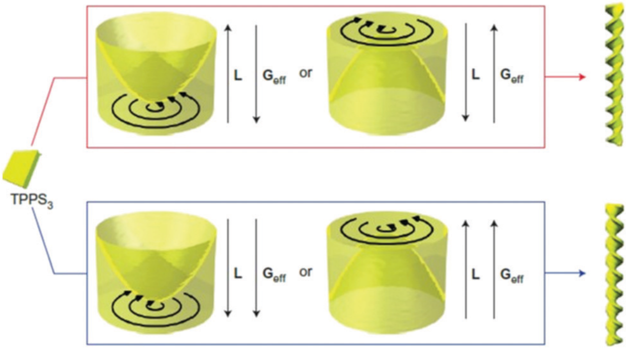

Fig. 5 Control of the handedness of TPPS$_3$ helical assemblies by the relative orientation of the angular momentum of rotation ($L$) and the effective gravity ($G_{\text{eff}}$). TPPS$_3$: tris-(4-sulfonatophenyl)phenyl porphyrin. Reprinted from ref. 161 with permission from Nature publishing group, copyright 2012.

**(e) Through plasma-triggered chemical reactions.** Plasma, produced by the impact of extra-terrestrial objects on earth, has been investigated as a potential source of asymmetry. Price and Furukawa teams reported, in 2013 and 2015, respectively, that nucleobases and/or proteinogenic amino acids were formed under conditions which presumably reproduced the conditions of impact of celestial bodies on primitive earth.[162,163] When shocked with a steel projectile fired at high velocities in a light gas gun, ice mixtures made of $NH_4OH$, $CO_2$ and $CH_3OH$, were found to produce equal amounts of (*R*)- and (*S*)-alanine, α-aminoisobutyric acid and isovaline as well as their precursors.[162] Importantly, only the impact shock is responsible for the formation of amino-acids because post-shot heating is not sufficient. A richer variety of organic molecules, including nucleobases, were obtained by shocking ammonium bicarbonate solution under nitrogen (representative of the Hadean ocean and its atmosphere) with various metallic projectiles (as simplified meteorite materials).[163] The production of amino-acids is correlated with the concentration of ammonium bicarbonate, acting as the C1-source. The attained pressure and temperature (up to 60 GPa and thousands Kelvin) allowed chemical reactions to proceed, as well as racemization as evidenced later,[164] but were not enough to trigger plasma processes. A meteorite impact was reproduced in the laboratory by Wurz and co-workers in 2016,[165] by firing projectiles of pure $^{13}$C synthetic diamond to a multilayer target consisting of ammonium nitrate, graphite and steel. The impact generated a pressure of 170 GPa and a temperature of 3 to 4 × $10^4$ K, enough to form a plasma torch, through the interaction between the projectile and target materials and their subsequent atomization and ionization. The most striking result is certainly the formation of $^{13}$C-enriched alanine which is claimed to be obtained with e.e. values ranging from 7 to 25%. The exact source of asymmetry is uncertain: the far-from-equilibrium nature of the plasma-triggered reactions and the presence of spontaneously generated electromagnetic fields in the reactive plasma torch may have led to the observed chiral biases.[166] This first report of an impact-produced enantio-enrichment needs to be confirmed experimentally and supported theoretically.

### 3.2 Polarized radiations and spins

**(a) Circularly polarized light (CPL).** A long time before the discussions on the true or false chiral nature of physical fields, Le Bel and van't Hoff already proposed, at the end of the nineteenth century, to use circularly polarized light, a truly chiral electromagnetic wave existing in two enantiomorphic forms (*i.e.* the left- and right-handed CPL), as chiral bias to induce enantiomeric excess.[31,167–169] Cotton strengthened this idea in 1895,[170–172] when he reported the circular dichroism (CD) of an aqueous solution of potassium chromium(III) tartrate.

Circular dichroism is a phenomenon, corresponding to the differential absorption of l-CPL and r-CPL at a given wavelength in the absorption region of an optically active material, as well the spectroscopic method that measures it.[173,174] Enantiomers absorbing CPL of one handedness constitute non-degenerated diastereoisomeric systems, based on the interaction between two distinct chiral influences, one chemical and the other physical. Thus, one state of this system is energetically favoured, and one enantiomer preferentially absorbs CPL of one polarization state (l- or r-CPL).

The dimensionless Kuhn anisotropy (or dissymmetry) factor $g$ allows the quantitative description of the chiroptical response of enantiomers (eqn (1)). The Kuhn anisotropy factor is expressed by the ratio between the difference in molar extinction coefficients of l-CPL and r-CPL ($\Delta\varepsilon$), and the global molar extinction coefficient ($\varepsilon$), where $\varepsilon_L$ and $\varepsilon_R$ are the molar extinction coefficients for left- and right-handed CPL, respectively.[175] It ranges from −2 to +2, for a total absorption of right- and left-handed CPL, respectively, and is wavelength dependent. Enantiomers have equal but opposite $g$ values, corresponding to their preferential absorption of one CPL handedness.

$$g = \frac{\Delta\varepsilon}{\varepsilon} = \frac{\varepsilon_L - \varepsilon_R}{\left(\frac{\varepsilon_L + \varepsilon_R}{2}\right)} \tag{1}$$

The preferential excitation of one over the other enantiomer in the presence of CPL allows the emergence of a chiral imbalance from a racemate (by asymmetric photoresolution or photolysis) or from rapidly interconverting chiral conformations (by asymmetric photosynthesis).[176–178] Asymmetric photolysis is based on the irreversible photochemical consumption of one enantiomer at a higher rate, within a racemic mixture which does not racemize during the process (Fig. 6a). In most cases, the (enantio-enriched) photo products are not identified. Thereby, the enantioenrichment comes from the accumulation of the slowly reacting enantiomer. It depends both on the unequal molar extinction coefficients ($\varepsilon_R$ and $\varepsilon_S$) for CPL of the (*R*)- and (*S*)-enantiomers, governing the different rate constants, as well as the extent of reaction $\xi$. Asymmetric photoresolution occurs within a mixture of enantiomers that interconvert in their excited states (Fig. 6b). Since the reverse reactions, from the excited to the ground states, should not be enantiodifferentiating, the deviation from the racemic mixture is only due to the difference of extinction coefficients ($\varepsilon_R$ and $\varepsilon_S$). While the total concentration in enantiomers ($C_R + C_S$) is constant during photoresolution, the photostationary state ($p_{ss}$) is reached after prolonged irradiation irrespective of the initial enantiomeric composition.[177] In the absence of side reactions, the $p_{ss}$ is reached for $\varepsilon_R C_R = \varepsilon_S C_S$, which allows e.e. $p_{ss}$ to be determined, e.e. at the photostationary state, as being equal to $(C_R - C_S)/(C_R + C_S) = g/2$. Asymmetric photosynthesis (also called asymmetric fixation) produces an enantio-enriched product by preferentially reacting one enantiomer of a substrate undergoing fast racemization (Fig. 6c). Under these conditions, the (*R*)/(*S*) ratio of the product is equal to the excitation ratio $\varepsilon_R/\varepsilon_S$, and the e.e. of the photoproduct is thus equal to $g/2$. The chiral bias which can be reached in asymmetric photosynthesis and photoresolution processes is thus related to the $g$ value of enantiomers, whereas the e.e. in asymmetric photolysis is influenced by both $g$ and $\xi$ values.

The first CPL-induced asymmetric partial resolution dates back to 1968 thanks to Stevenson and Verdieck, who worked with octahedral oxalato complexes of chromium(III).[179] Asymmetric photoresolution was further investigated for small organic molecules,[180,181] macromolecules[182] and supramolecular assemblies.[183] A number of functional groups such as overcrowded alkene, azobenzene, diarylethene, α,β-unsaturated ketone or fulgide were specifically-designed to enhance the efficiency of the photoresolution process.[58]

Kagan *et al.* pioneered the field of asymmetric photosynthesis with CPL in 1971, through examining hexahelicene photocyclization in the presence of iodine.[184] The following year, Calvin *et al.* reported an e.e. of up to 2% for an octahelicene produced under similar conditions.[185] Enantioenrichment by photoresolution and photosynthesis with CPL is limited in scope, since it requires molecules with high $g$ values to be detected, and in intensity, since it is limited to $g/2$.

Since its discovery by Kuhn *et al.* ninety years ago,[186,187] through the enantioselective decomposition of ethyl-α-bromopropionate and *N*,*N*-dimethyl-α-azidopropionamide, the asymmetric photolysis of racemates has attracted a lot of interest. In the common case of two competitive pseudo-first order photolytic reactions with unequal rate constants, $k_S$ and $k_R$, for the (*S*) and (*R*) enantiomers, respectively, and if the anisotropies are close to zero, the enantiomeric excess induced by

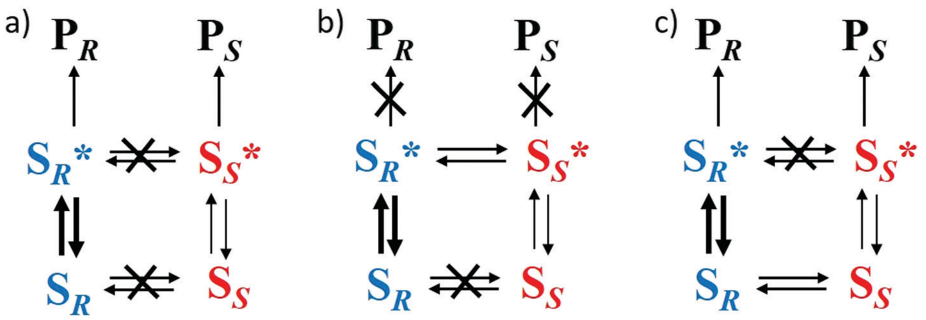

Fig. 6 Simplified kinetic schemes for asymmetric (a) photolysis, (b) photoresolution and (c) photosynthesis with CPL. $S_R$ and $S_S$ are substrate enantiomers and $S_R^*$ and $S_S^*$ are their photoexcited states. $P_R$ and $P_S$ are the products generated from the respective photoexcited states. The thick line represents the preferential absorption of CPL by one of the enantiomers. $[S_S] > [S_R]$ for asymmetric photolysis and photoresolution processes whilst $[P_R] > [P_S]$ for asymmetric photosynthesis.

asymmetric photolysis can be approximated as eqn (2):[188]

$$\text{e.e.} \geq \left(1-(1-\xi)^{\frac{g}{2}}\right) \times 100(\%) \tag{2}$$

where $\xi$ is the extent of reaction.

In 1974, the asymmetric photodecomposition of racemic camphor reported by Kagan *et al.* reached 20% e.e. at 99% completion, a long-lasting record in this domain.[189] Three years later, Norden[190] and Bonner *et al.*[191] independently showed that enantioselective photolysis by UV-CPL was a viable source of symmetry-breaking for amino acids, by inducing an e.e. of up to 2% in aqueous solutions of alanine and glutamic acid,[191] or 0.2% with leucine.[190] Leucine was then intensively studied thanks to a relatively high anisotropy factor in the UV region.[192] The *e.e.* was increased up to 1.3% in 2001 ($\xi$ = 0.55) by Inoue *et al.* by exploiting the pH-dependence of the $g$ value.[193,194] In the early 2000s, Meierhenrich *et al.* got closer to astrophysically relevant conditions by irradiating samples in the solid state with synchrotron vacuum ultraviolet (VUV)-CPL (below 200 nm). This made it possible to avoid water absorption in the VUV, and allowed electronic transitions having higher anisotropy factors to be reached (Fig. 7).[195] In 2005, a solid racemate of leucine was reported to reach 2.6% of e.e. after illumination with r-CPL at 182 nm ($\xi$ not reported).[196] More recently, the same team improved the selectivity of the photolysis process, thanks to amorphous samples of finely-tuned thickness, providing e.e. values of 5.2 ± 0.5% and 4.2 ± 0.2% for leucine,[197] and alanine,[198,199] respectively. A similar enantioenrichment was reached in 2014 with gaseous photo-ionized alanine,[200] which constitutes an appealing result taking into account the detection of interstellar gases such as propylene oxide[201] and glycine[202] in star-forming regions.

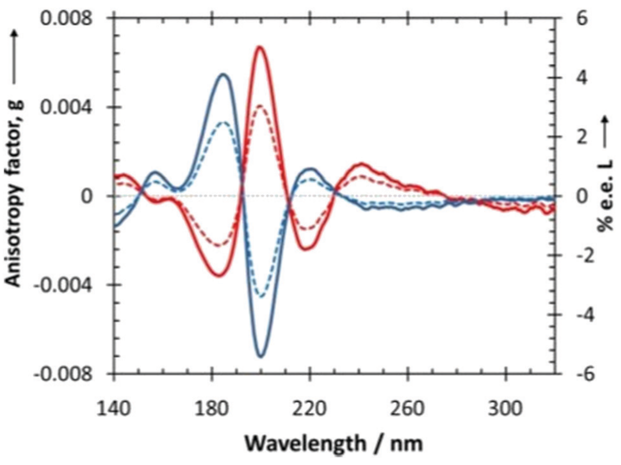

Fig. 7 Anisotropy spectra (thick lines, left ordinate) of isotropic amorphous (*R*)-alanine (red) and (*S*)-alanine (blue), in the VUV and UV spectral regions. Dashed lines represent the enantiomeric excess (right ordinate) that can be induced by photolysis of *rac*-alanine with either left- (in red) or right- (in blue) circularly polarized light at $\xi$ = 0.9999. Positive e.e. values correspond to scalemic mixture biased in favour of (*S*)-alanine. Note that enantiomeric excesses are calculated from eqn (2). Reprinted from ref. 192 with permission from Wiley-VCH, copyright 2017.

Important studies in the context of BH reported the direct formation of enantio-enriched amino acids generated from simple chemical precursors, when illuminated with CPL. Takano *et al.* showed in 2007 that eleven amino acids could be generated upon CPL irradiation of macromolecular compounds, originating from proton-irradiated gaseous mixtures of CO, $NH_3$ and $H_2O$.[203] Small e.e. values of +0.44 ± 0.31% and −0.65 ± 0.23% were detected for alanine upon irradiation with r- and l-CPL, respectively. Nuevo *et al.* irradiated interstellar ice analogues composed of $H_2O$, $^{13}CH_3OH$ and $NH_3$ at 80 K with CPL centred at 187 nm, which led to the formation of alanine with an e.e. of 1.34 ± 0.40%.[204] The same team also studied the effect of CPL on regular ice analogues or organic residues coming from their irradiation in order to mimic the different stages of asymmetric induction in interstellar ices.[205] Sixteen amino acids were identified, and five of them (including alanine and valine) were analysed by enantioselective two-dimensional gas chromatography, GC × GC,[206] coupled to TOF mass spectrometry, to show enantioenrichments of up to 2.54 ± 0.28% e.e. Optical activities likely originated from the asymmetric photolysis of the amino acids initially formed as racemates. Advantageously, all five amino acids exhibited e.e. values of identical sign for a given polarization and wavelength, suggesting that irradiation by CPL could constitute a general route towards amino acids with a single chirality. Even though the chiral biases generated upon CPL irradiation are modest, these values can be significantly amplified through different physicochemical processes, notably those including auto-catalytic pathways (see Parts 4 and 5).

**(b) Spin-polarized particles.** In the cosmic scenario, it is believed that the action of polarized quantum radiation in space, such as circularly polarized photons or spin-polarized particles, may have induced asymmetric conditions in the primitive interstellar media resulting in terrestrial bioorganic homochirality. In particular, nuclear-decay- or cosmic-ray-derived leptons (*i.e.* electrons, muons, and neutrinos) in nature have a specified helicity, that is, they have a spin angular momentum polarized parallel or antiparallel to their kinetic momentum due to parity violation (PV) in the weak interaction (Part 2).

Of the leptons, electrons are one of the most universally present particles in ordinary materials. Spin-polarized electrons in nature are emitted with $\beta^-$ decay from radioactive nuclear particles derived from PV involving the weak nuclear interaction and spin-polarized positrons (the anti-particle of electrons) from $\beta^+$ decay. In $\beta^-/\beta^+$-decay, with weak interaction, the spin angular momentum vectors of electrons/positrons are perfectly polarized as antiparallel/parallel to the vector direction of the kinetic momentum. In this meaning, spin-polarized electrons/positrons are "chiral radiation", as well as are muons and neutrinos, which will be mentioned below. It is expected that spin-polarized leptons will induce reactions different from those triggered by CPL. For example, $\beta^-$ decay from $^{60}Co$ is accompanied by circularly polarized gamma-rays.[207] Similarly, spin-polarized muon irradiation has the potential to induce novel types of optical activities different from those of polarized photon and spin-polarized electron irradiation.

Single-handed polarized particles produced by supernovae explosions may thus interact with molecules in the proto-solar clouds.[35,207–210] Left-handed electrons generated by $\beta^-$-decay impinge on matter to form a polarized electromagnetic radiation through bremsstrahlung. At the end of fifties, Vester and Ulbricht suggested that these circularly-polarized "Bremsstrahlen" photons can induce and direct asymmetric processes towards a single direction upon interaction with organic molecules.[107,211] From the sixties to the eighties,[212–220] many experimental attempts to show the validity of the "V–U hypothesis", generally by photolysis of amino acids in the presence of a number of β-emitting radionuclides or through self-irradiation of $^{14}$C-labeled amino acids, only led to poorly conclusive results.[44,221,222] During the same period, the direct effect of high-energy spin-polarized particles (electrons, protons, positrons and muons) has been probed for the selective destruction of one amino acid enantiomer in a racemate, but without further success as reviewed by Bonner.[44,54] More recent investigations by the international collaboration RAMBAS (RAdiation Mechanism of Biomolecular ASymmetry) claimed minute e.e. values (up to 0.005%) upon irradiation of various amino acid racemates with (natural) left-handed electrons.[223,224]

Other fundamental particles have been proposed to play a key role in the emergence of BH.[207,209,225] Amongst them, electron antineutrinos have received particular attention, through the Supernova Neutrino Amino Acid Processing (SNAAP) model.[226–228] Electron antineutrinos are emitted after a supernova explosion, to cool the nascent neutron star, and, by a similar reasoning to that applied with neutrinos, they are all right-handed. According to the SNAAP scenario, right-handed electron antineutrinos generated in the vicinity of neutron stars with strong magnetic and electric fields were presumed to selectively transform $^{14}$N into $^{14}$C, and this process depended on whether the spin of $^{14}$N was aligned or anti-aligned with that of the antineutrinos. Calculations predicted enantiomeric excesses for amino acids from 0.02% to a few percent, and a preferential enrichment in (*S*)-amino acids.

Despite important efforts, no experimental evidence has been reported to date in favour of a deterministic scenario for the generation of a chiral bias in prebiotic molecules.

**(c) Chirality induced spin selectivity (CISS).** An electron in helical roto-translational motion with spin–orbit coupling (i.e. translating in a "ballistic" motion with its spin projection parallel or antiparallel to the direction of propagation) can be regarded as chiral, existing as two possible enantiomers, corresponding to the α and β spin configurations, which do not coincide upon space and time inversion. Such peculiar "chiral actor" is the object of spintronics, the fascinating field of modern physics which deals with the active manipulation of spin degrees of freedom of charge carriers.[230] The interaction between polarized spins of secondary electrons (SEs) and chiral molecules leads to chirality induced spin selectivity (CISS), a recently reported phenomenon.

In 2008, Rosenberg *et al.*[231] irradiated adsorbed molecules of (*R*)-2-butanol or (*S*)-2-butanol on a magnetized iron substrate with low-energy SEs (10–15% of spin polarization) and measured a difference of about ten percent in the rate of CO bond cleavage of the enantiomers. Extrapolations of the experimental results suggested that an e.e. of 25% would be obtained after photolysis of the racemate at 98.6% of conversion. Importantly, the different rates in the photolysis of the 2-butanol enantiomers depend on the spin polarization of SEs, showing the first example of CISS.[232–234] Later, SEs with a higher degree of spin polarization (60%) were found to dissociate Cl from epichlorohydrin (Epi) with a quantum yield 16% greater for the *S* form.[229] To achieve this, electrons are produced by X-ray irradiation of a gold substrate and spin-filtered by a self-assembled overlayer of DNA before they reach the adlayer of Epi (Fig. 8).

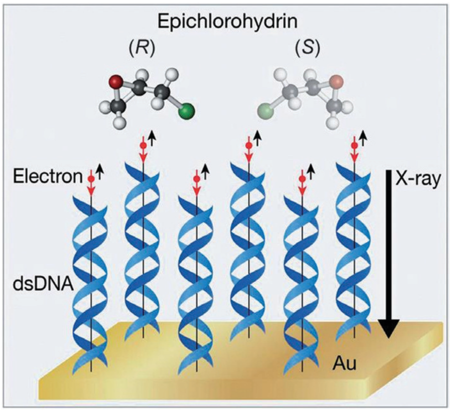

Fig. 8 Enantioselective dissociation of epichlorohydrin by spin polarized SEs. Red (black) arrows indicate the electron's spin (motion direction, respectively). Reprinted from ref. 229 with permission from Wiley-VCH, copyright 2015.

In 2018, Banerjee-Ghosh *et al.* showed that a magnetic field perpendicular to a ferromagnetic (FM) substrate can generate enantioselective adsorption of polyalanine, ds-DNA and cysteine.[235] One enantiomer was found to be more rapidly adsorbed on the surface depending on the magnetization direction (Fig. 9). The effect is not attributed to the magnetic field *per se* but to the exchange interaction between the adsorbed molecules and surface electron spins, *i.e.* CISS.

Enantioselective crystallization of initially racemic mixtures of asparagine, glutamic acid, and threonine, known to crystallize as conglomerates, was also observed on a ferromagnetic substrate surface (Ni(120 nm)/Au(10 nm)).[230] The racemic mixtures were crystallized from aqueous solution on the ferromagnetic surfaces in the presence of two magnets, one pointing north and the other south, located at different sites of the surface. A clear enantioselective effect was observed in the formation of an excess of D- or L-crystals, depending on the direction of the magnetization orientation.

In 2020, the CISS effect was successfully applied to several asymmetric chemical processes, SEs acting as chiral reagents.[236] Spin-polarized electrons, produced by a magnetized Ni/Au substrate coated with an achiral self-assembled monolayer (SAM) of carboxyl-terminated alkanethiols [$\mathrm{HS{-}(CH_2)_{x-1}{-}COO^-}$], caused an enantiospecific association of 1-amino-2-propanol enantiomers, leading to an e.e. of 20% in the reactive medium.

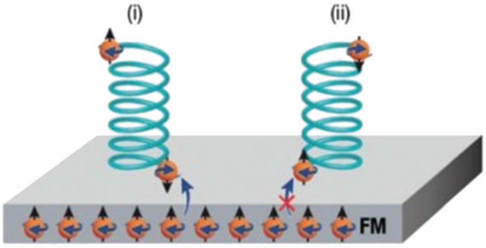

Fig. 9 Suggested mechanism for the enantiospecific interaction triggered by chiral-induced spin selectivity. Enantiomers are sketched as opposite green helices and electrons as orange spheres with straight arrows indicating their spin orientation, which can be reversed for surface electrons by changing the magnetization direction. In contact with the perpendicularly magnetized FM surface, molecular electrons are redistributed to form a dipole, and the spin orientation at each pole depends on the chiral potentials of enantiomers. The interaction between the FM substrate and the adsorbed molecule (blue arrows) is favoured when the two spins are antiparallel leading to the preferential adsorption of one enantiomer over the other. Reprinted from ref. 230 with permission from the Royal Society of Chemistry, copyright 2019, under Creative Commons Attribution 3.0 Unported License https://creativecommons.org/licenses/by/3.0/.

The enantioselective electro-reduction of (1*R*/1*S*)-10-camphorsulfonic acid (CSA) into isoborneol was also governed by the spin orientation of SEs, injected through an electrode, with an e.e. of about 11.5% after the electrolysis of 80% of the initial amount of CSA.

Electrochirogenesis links the CISS process to biological homochirality through several theories, all based on an initial bias stemming from spin polarized electrons.[232,237] Strong fields and radiations of neutron stars could align ferrous magnetic domains in interstellar dust particles, and produce spin-polarized electrons, able to create an enantiomeric excess into adsorbed chiral molecules. One enantiomer from a racemate in a cosmic cloud would merely accrete on a magnetized domain in an enantioselective manner as well. Alternatively, magnetic minerals of the prebiotic world, like pyrite ($FeS_2$) or greigite ($Fe_3S_4$), might serve as an electrode in the asymmetric electrosynthesis of amino acids or purines, or as a spin filter in the presence of an external magnetic field, *e.g.* in hydrothermal vents.

### 3.3 Chiral surfaces

**(a) Inorganic minerals and clays.** Chiral surfaces constitute unequivocal true asymmetry sources that are widespread over the earth surface in the form of various minerals, α-quartz, calcite, gypsum, and some clays notably. The implication of chiral surfaces in the context of BH has been debated[44,238–242] along two main axes: (i) the preferential adsorption of prebiotically relevant molecules, and (ii) the potential unequal distribution of left-handed and right-handed surfaces for a given mineral or clay on the earth surface.

Selective adsorption is generally the consequence of reversible and preferential diastereomeric interactions between the chiral surface and one of the enantiomers,[239] commonly described by the simple three-point model. But this model, assuming that only one enantiomer can present three groups that match three active positions of the chiral surface,[243] fails to fully explain chiral recognition which are the fruit of more subtle interactions.[244] In the second part of the XXth century, a large number of studies have focused on demonstrating chiral interactions between biological molecules and inorganic mineral surfaces.

Quartz is the only common mineral which is composed of enantiomorphic crystals. Right-handed (D-quartz) and left-handed (L-quartz) can be separated (similarly to the tartaric acid salts of the famous Pasteur experiment) and investigated independently in adsorption studies of organic molecules. The process of separation is made somewhat difficult by the presence of "Brazilian twins" (also called chiral or optical twins),[242] which might bias the interpretation of the experiments. Bonner *et al.* in 1974[245,246] measured the differential adsorption of alanine derivatives defined as % adsorbed on D-quartz − % adsorbed on L-quartz. These authors reported on the small but significant 1.4 ± 0.4% preferential adsorption of (*R*)-alanine over D-quartz and (*S*)-alanine over L-quartz, respectively. A more precise evaluation of the selectivity with radiolabelled (*RS*)-alanine hydrochloride led to higher levels of differential adsorption between L-quartz and D-quartz (up to 20%).[247] The hydrochloride salt of alanine isopropyl ester was also found to be adsorbed enantiospecifically from its chloroform solution leading to chiral enrichment varying between 1.5 and 12.4%.[248] Furuyama and co-workers also found preferential adsorption of (*S*)-alanine and (*S*)-alanine hydrochloride over L-quartz from their ethanol solutions.[249,250] Anhydrous conditions are required to get sufficient adsorption of the organic molecules onto α-quartz crystals which, according to Bonner, discards α-quartz as a suitable mineral for the deracemization of building blocks of life.[251] According to Hazen and Scholl,[239] the fact that these studies have been conducted on powdered quartz crystals (*i.e.* polycrystalline quartz) has hampered a precise determination of the mechanism and magnitude of adsorption on specific surfaces of α-quartz. Some of the faces of quartz crystals likely display opposite chiral preferences which may have reduced the experimentally-reported chiral selectivity. Moreover, chiral indices of the commonest crystal growth surfaces of quartz, as established by Downs and Hazen, are relatively low (or zero), suggesting that the potential of enantiodiscrimination of organic molecules by quartz is weak in overall.[252] Quantum-mechanical studies using density functional theories (DFT) have also been performed to probe the enantiospecific adsorption of various amino acids on hydroxylated quartz surfaces.[253–256] In short, the computed differences in the adsorption energies of the enantiomers are modest (on the order of 2 kcal $mol^{-1}$ at best) but strongly depend on the nature of amino acids and quartz surfaces. A final argument against the implication of quartz as a deterministic source of chiral discrimination of the molecules of life comes from the fact that D-quartz and L-quartz are equally distributed on earth.[257,258]

Calcite ($CaCO_3$), as the most abundant marine mineral in the Archaean era, has potentially played an important role in the formation of prebiotic molecules relevant to life. The trigonal scalenohedral crystal form of calcite displays chiral faces which can yield chiral selectivity. In 2001, Hazen *et al.*[261] reported that (*S*)-aspartic acid adsorbs preferentially on the $(3\bar{1}\bar{2}1)$ face of calcite, whereas (*R*)-aspartic acid adsorbs preferentially on the $(21\bar{3}1)$ face. An e.e. value in the order of 0.5% on average was measured for the adsorbed aspartic acid molecules. No selectivity was observed on a centric surface that served as control. The experiments were conducted with aqueous solutions of (*rac*)-aspartic acid and selectivity was greater on crystals with terraced surface textures, presumably because enantiomers concentrated along step-like linear growth features. The calculated chiral indices of the (214) scalenohedral face of calcite was found to be the highest amongst 14 surfaces selected from various minerals (calcite, diopside, quartz, and orthoclase) and face-centred cubic (FCC) metals.[252] In contrast, DFT studies revealed negligible difference in adsorption energies of enantiomers ($<1$ kcal mol$^{-1}$) of alanine on the $(21\bar{3}1)$ face of calcite because alanine cannot establish three points of contact on the surface.[262] Conversely, it is well established that amino acids modify the crystal growth of calcite crystals in a selective manner leading to asymmetric morphologies, *e.g.* upon crystallization[263,264] or electrodeposition (Fig. 10a).[259] Vaterite helicoids, produced by crystallization of $CaCO_3$ in the presence of non-racemic mixtures of aspartic acid, were found to be single-handed (Fig. 10b).[260] Enantiomeric ratio are identical in the helicoids and in solution, *i.e.* incorporation of aspartic acid in valerite displays no chiral amplification effect. Asymmetric growth was also observed for various organic substances with gypsum, another mineral with a centrosymmetric crystal structure.[265] As expected, asymmetric morphologies produced from amino acid enantiomers are mirror image (Fig. 10).

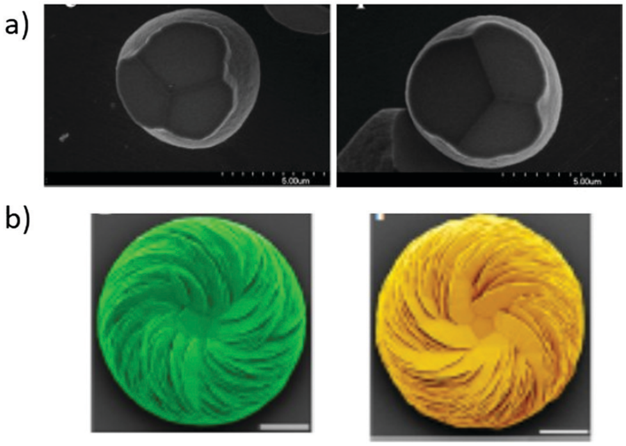

Fig. 10 Asymmetric morphologies of $CaCO_3$-based crystals induced by enantiopure amino acids. (a) Scanning electron micrographs (SEM) of calcite crystals obtained by electrodeposition from calcium bicarbonate in the presence of magnesium and (*S*)-aspartic acid (left), and (*R*)-aspartic acid (right). Reproduced with permission from ref. 259. Copyright 2007. American Chemical Society. (b) SEM images of vaterite helicoids obtained by crystallization in the presence of non-racemic solutions (40% e.e.) biased in favour of (*S*)-aspartic acid (left) and (*R*)-aspartic acid (right). Reprinted from ref. 260. Copyright 2019. Springer Nature under Creative Commons Attribution 4.0 International License https://creativecommons.org/licenses/by/4.0/.

Clay minerals, of which some of them display high specific surface area, and adsorption and catalytic properties, are often invoked as potential promoters of the transformation of prebiotic molecules. Amongst the large variety of clays, serpentine and montmorillonite were likely the dominant ones on earth prior to life's origin.[241] Clay minerals can exhibit non-centrosymmetric structures, such as the A and B forms of kaolinite, which correspond to the enantiomeric arrangement of the interlayer space. These chiral organizations are, however, not individually separable. All experimental studies claiming asymmetric inductions by clay minerals reported in the literature have raised suspicion about their validity, with no exception.[242] This is because these studies employed either a racemic clay or clays which have no established chiral arrangement, *i.e.* presumably achiral clay minerals. Asymmetric adsorption and polymerization of amino acids reported with kaolinite[266–270] and bentonite[271–273] in the 1970s–1980s actually originated from experimental errors or contaminations. Supposedly enantiospecific adsorptions of amino acids with allophane,[274] hydrotalcite-like compound,[275] montmorillonite,[276] and vermiculite[277,278] also likely belong to this category.

Experiments aimed at demonstrating deracemization of amino acids in the absence of any chiral inducers or during phase transition under equilibrium conditions have to be interpreted cautiously (see the Chapter 4.2 of the book written by Meierhenrich for a more comprehensive discussion on this topic).[24] Deracemization is possible under far-from-equilibrium conditions but a set of repeated experiments must then reveal a distribution of the chiral biases (see Part 4). The claimed specific adsorptions for racemic mixtures of amino acids likely originated from the different purities between (*S*)- and (*R*)-amino acids; or contaminants of biological origin such as microbial spores.[279] Such issues are not old-fashioned and despite great improvement in analytical and purification techniques, the difference in enantiomer purities is most likely at the origin of the different behaviour of amino acid enantiomers observed in the crystallization of wulfingite ($\varepsilon$-$Zn(OH)_2$)[280] and $CaCO_3$[281,282] in two recent reports.

Very impressive levels of selectivity (on the range of 10% e.e.) were recently reported for the adsorption of aspartic acid on brushite, a mineral composed of achiral crystals of $CaHPO_4\cdot 2H_2O$.[283] In this case, selective adsorption was observed under supersaturation and undersaturation conditions (*i.e.* non-equilibrium states) but not at saturation (equilibrium state). Likewise, opposite selectivity was observed for the two non-equilibrium states. It was postulated that mirror symmetry breaking of the crystal facets occurred during the dynamic events of crystal growth and dissolution. Spontaneous mirror symmetry breaking is not impossible under far-from-equilibrium conditions but again a distribution of the selectivity outcome is expected upon repeating the experiments under strictly achiral conditions (Part 4).

Ribó and co-workers proposed that chiral surfaces could have been involved in the chiral enrichment of prebiotic molecules on carbonaceous chondrites present on meteorites.[284] In their scenario, mirror symmetry breaking during the formation of planetesimal bodies and comets may have led to a bias in the distribution of chiral fractures, screw distortions or step-kink chiral centres on the surfaces of these inorganic matrices. This in turn would have led to a bias in the adsorption of organic compounds. Their study was motivated by the fact that the enantiomeric excesses measured for organic molecules vary according to their location on the meteorite surface.[285] Their measurement of the optical activity of three meteorite samples by circular birefringence (CB) indeed revealed a slight bias towards negative CB values for the Murchinson meteorite. The optically active areas are attributed to serpentines and other poorly identified phyllosilicate phases, whose formation may have occurred concomitantly to organic matter.

The implication of inorganic minerals in biasing the chirality of prebiotic molecules remains uncertain given that no strong asymmetric adsorption values have been reported to date and that certain minerals were even found to promote the racemization of amino acids[286] and secondary alcohols.[287] However, evidence exists that minerals could have served as hosts and catalysts for prebiotic reactions, including the polymerization of nucleotides.[288] In addition, minute chiral biases provided by inorganic minerals could have driven SMSB processes into a deterministic outcome (Part 4).

**(b) Organic crystals.** Organic crystals may have also played a role in biasing the chirality of prebiotic chemical mixtures. Along this line, glycine appears as the most plausible candidate given its probable dominance over more complex molecules in the prebiotic soup.

α-Glycine crystallizes from water into a centrosymmetric form. In the 1980s, Lahav, Leiserowitch and co-workers demonstrated that amino acids were occluded to the basal faces (010 and 0$\bar{1}$0) of glycine crystals with exquisite selectivity.[289–291] For example, when a racemic mixture of leucine (1–2% wt/wt of glycine) was crystallized with glycine at an air/water interface, (*R*)-Leu was incorporated only into those floating glycine crystals whose (010) faces were exposed to the water solution, while (*S*)-Leu was incorporated only into the crystals with exposed (0$\bar{1}$0) faces. This results in the nearly perfect resolution (97–98% e.e.) of Leu enantiomers. In the presence of a small amount of an enantiopure amino-acid (*e.g.* (*S*)-Leu), all crystals of Gly exposed the same face to the water solution leading to one enantiomer of a racemate being occluded in glycine crystals while the other remains in solution. These striking observations led the same authors to propose a scenario in which the crystallization of supersaturated solutions of glycine in the presence of amino-acid racemates would have led to the spontaneous resolution of all amino acids (Fig. 11).

This can be considered as a "by chance" mechanism in which one of the enantiotopic face (010) would have been exposed preferentially to the solution in the absence of any chiral bias. From then, the solution, enriched into (*S*)-amino acids, enforces all glycine crystals to expose their (010) faces to water, eventually leading to all (*R*)-amino acids being occluded in glycine crystals.

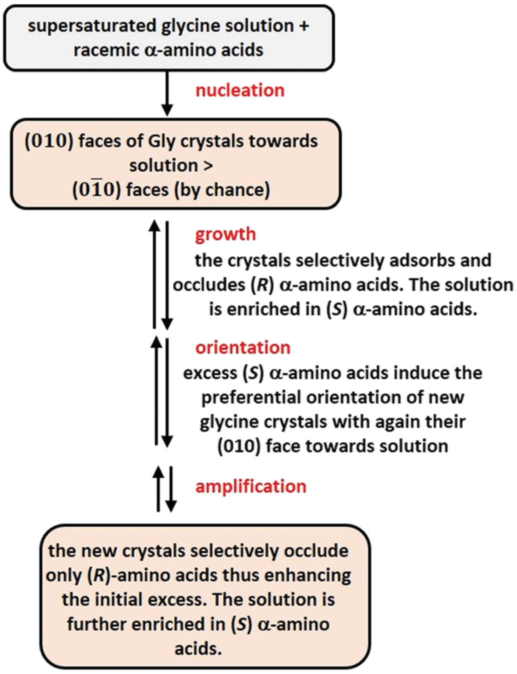

Fig. 11 Resolution of amino acid enantiomers following a "by chance" mechanism including enantioselective occlusion into achiral crystals of glycine.[289,290]

A somewhat related strategy was disclosed in 2010 by Soai and co-workers.[292] Dehydration of centrosymmetric crystals of cytosine monohydrate yielded enantio-enriched anhydrous cytosine chiral crystals when only one of two enantiotopic faces of the crystal was put into direct contact with the hot plate. Enrichment was also observed if the dehydration was performed under reduced pressure but with a surprising inversion of the configuration of the chiral crystal relative to thermal dehydration.[293] Rearrangement of the hydrogen bond network during transition between the centrosymmetric and chiral forms of the cytosine crystals is likely at the origin of this selective process. Reactions occurring at the enantiotopic surface of an organic crystal also yields enantio-enriched compounds whose optical purity can be enhanced by SMSB processes.[294,295]

**(c) Metal surfaces.** The last two decades have seen the emergence of chiral metal surfaces displaying high adsorption enantioselectivities.[239,244,296] The choice between metal surfaces can be oriented based on computational predictions of their enantiospecificity as reported recently for a variety of α-amino acids on Ag/Cu/Pd/Pt(531) surfaces.[297] Mechanisms leading to specific adsorptions on chiral metal surfaces can be well established. For example, the decomposition of tartaric acid, enantiospecifically adsorbed on Cu(651)$^{S}$ surfaces, follows non-linear kinetics, suggesting auto-catalysis.[298] Likewise, adsorption of scalemic mixtures of aspartic acid onto an achiral Cu(111) surface occurs with amplification of chirality, *i.e.* the e.e. of the adsorbed enantiomers of the surface is largely higher than the e.e. of enantiomers in the gas phase.[299] This effect, which presents some similarity to non-linear effects observed in asymmetric catalysis,[62] is related to the formation of homochiral adsorbate clusters. Auto-catalysis and chiral amplification are two key requirements for spontaneous mirror symmetry breaking (Part 4) and consequently such mechanistic studies on chiral metal surfaces may reveal important pathways towards homochirality.[300]

## 4. Spontaneous mirror-symmetry breaking (SMSB)

### 4.1 Definition, models and the Soai reaction

Spontaneous mirror-symmetry breaking (SMSB) phenomenon is the process that leads to the preferential formation of one chiral state over its enantiomeric form in the absence of a detectable chiral bias or enantiomeric imbalance. As defined by Ribó and co-workers, SMSB concerns the transformation of "metastable racemic non-equilibrium stationary states (NESS) into one of two degenerate but stable enantiomeric NESSs".[301] Although this definition is somewhat in contradiction with the textbook statement that enantiomers need the presence of a chiral bias to be distinguished, it was recognized a long time ago that SMSB can emerge from reactions involving asymmetric self-replication or auto-catalysis. The connection between SMSB and BH is appealing,[25,40,51,301–308] since SMSB is the unique physicochemical process that allows for the emergence and retention of enantiopurity from scratch. It is also intriguing to note that the competitive chiral reaction networks that might give rise to SMSB could exhibit replication, dissipation and compartmentalization,[301,309] *i.e.* fundamental functions of living systems.

Systems able to lead to SMSB consist of enantioselective autocatalytic reaction networks, described through models dealing with either the transformation of achiral to chiral compounds, or the deracemization of racemic mixtures.[301] As early as 1953, Frank described a theoretical model dealing with the former case. According to Frank's model, SMSB emerges from a system involving homochiral self-replication (one enantiomer of the chiral product accelerates its own formation) and heterochiral inhibition (the replication of the other product enantiomer is prevented).[303] It is now well-recognized that the Soai reaction,[56] an auto-catalytic asymmetric process (Fig. 12a), disclosed 42 years later,[310] is an experimental validation of the Frank model. The reaction between pyrimidine-5-carbaldehyde and diisopropyl zinc (two achiral reagents) is strongly accelerated by their zinc alkoxy product, which is found to be enantiopure (>99% e.e.) after a few cycles of reaction/addition of reagents (Fig. 12b and c).[310–312] Kinetic models based on the stochastic formation of homochiral and heterochiral dimers[313–315] of the zinc alkoxy product provide good fits of the kinetic profile even though the involvement of higher species has gained more evidence recently.[316–324] In this model, homochiral dimers serve as auto-catalysts for the formation of the same enantiomer of the product whilst heterochiral dimers are inactive and sequester the minor enantiomer, a Frank model-like inhibition mechanism. A hallmark of the Soai reaction is that the direction of auto-catalysis is dictated by extremely weak chiral perturbations: quartz, cryptochiral molecules, circularly polarized light, and chiral isotopomers amongst others (Fig. 12b).[312] In addition, the apparent outcome of the Soai reaction performed in the absence of detectable chiral species is stochastic as expected for a truly SMSB process (Fig. 12c).[325–333] On the one hand, the Soai reaction offers a credible mechanistic scenario from which homochiral biomolecules at the origin of life would have been created on a deterministic manner through a SMSB process coupled to an infinitesimal chiral bias (*vide infra*). This bias would have survived from a larger one despite significant erosion through racemization processes. On the other hand, the Soai reaction is more an exception than a rule in the chemical space explored to date.[334–342] The exergonic and irreversible nature of the organozinc addition reaction are key for pushing the system far-from-equilibrium and for the generation and preservation of the homochiral state. On the contrary, it is assumed that prebiotic chemical reactions would have been only weakly exergonic, *i.e.* their products would have been more prone to racemization or to side reactions occurring in solution.[37,46,301]

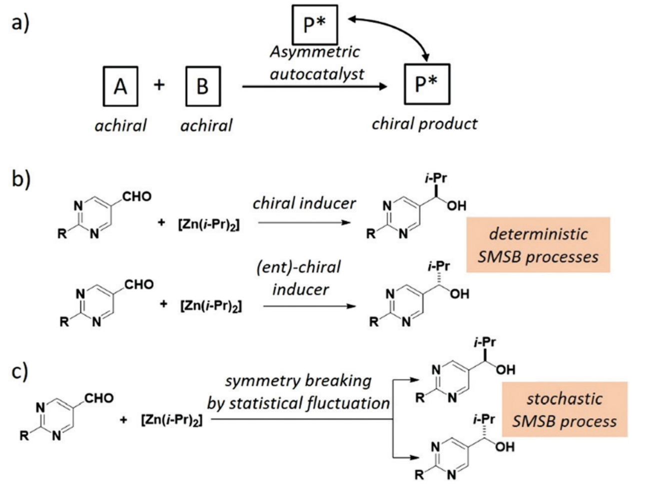

Fig. 12 (a) General scheme for an auto-catalysed asymmetric reaction. (b) The Soai reaction performed in the presence of detected chirality, leading to highly enantio-enriched alcohol with the same configuration in successive experiments (deterministic SMSB). (c) Soai reaction performed in the absence of detected chirality, leading to highly enantio-enriched alcohol with a bimodal distribution of the configurations in successive experiments (stochastic SMSB).

Many other models of spontaneous emergence of homochirality in far-from-equilibrium systems have been proposed in the literature.[343–345] Most of them are derived from the Frank model but do not include any mutual inhibition reaction. The limited enantioselective (LES) model[306,346] assumes that both the asymmetric auto-catalysis (similar to the homochiral self-replication in the Frank model) and the non-enantioselective auto-catalysis (the accelerated formation of both enantiomers of the product) can co-exist. SMSB emerges if these two auto-catalytic processes are (i) individually compartmentalized within regions experiencing different temperatures,[347,348] or (ii) driven by a constant concentration of external reagents.[349] Required conditions for SMSB through the LES model could have been present in deep ocean hydrothermal plumes. Likewise, a chemical scenario has been proposed for LES based on coupled Strecker-type reactions for amino acid synthesis and degradation which have been postulated to be accelerated by a heterogeneous catalytic support such as phyllosilicates.[349] However, the LES model has found no experimental evidence to date. Models for enantioselective hypercyclic replicators were recently disclosed in which the inhibition reaction in the Frank model has been replaced by mutual cross-catalytic processes occurring between families of coupled replicators.[350,351] These models support a scenario in which the combination of SMSB, formation of the first (coupled) self-replicators and the emergence of their functions would have led to BH.[301] This intriguing concept may foster experimental investigations of SMSB processes in polymerization/depolymerization reactions.

Imposed boundary conditions for SMSB involve "either systems open to matter exchange, or closed systems unable to equilibrate energy with their surroundings".[301] In the absence of any chiral influence, the obtained metastable NESSs are exposed to statistical fluctuations, and evolve towards scalemic or homochiral NESSs, as long as the systems are far-from-equilibrium. It is important to note that in the absence of these boundary conditions, systems will be able to equilibrate with their surrounding and the deviation from the racemic state will be lost, *e.g.* racemization would occur under classically employed reaction workups operated in solution.[41,352] This is probably the main reason why a single SMSB process has been identified to date for a reaction performed in solution (the Soai reaction). On the contrary, SMSB processes have been observed more frequently in crystals (*vide infra*) or in supramolecular assemblies,[353] *i.e.* processes involving phase transition. Asymmetric reactions performed with catalytic single-handed supramolecular assemblies obtained through a SMSB process were found to yield enantio-enriched products whose configuration is left to chance.[157,354] SMSB processes leading to homochiral crystals as the final state appear particularly relevant in the context of BH and will thus be discussed separately in the following section.

### 4.2 Homochirality by crystallization

Havinga postulated that just one enantiomorph can be obtained upon a gentle cooling of a racemate solution (i) when the crystal nucleation is rare and the growth is rapid and (ii) when fast inversion of configuration occurs in solution (*i.e.* racemization). Under these circumstances, only monomers with matching chirality to the primary nuclei crystallize leading to SMSB.[55,355] Havinga reported in 1954 a set of experiments aimed at demonstrating his hypothesis with *N*,*N*,*N*-allylethylmethylanilinium iodide – an organic molecule which crystallizes as a conglomerate from chloroform (Fig. 13).[355] Fourteen supersaturated solutions were gently heated in sealed tubes, then stored at 0 °C to give crystals which were in 12 cases inexplicably more dextrorotatory (measurement of optical activity by dissolution in water, where racemization is not observed). Seven other supersaturated solutions were carefully filtered before cooling to 0 °C, but no crystallization occurred after one year. Crystallization occurred upon further cooling: three crystalline products with no optical activity were obtained, while the other four showed a small optical activity ($[\alpha]_D$ = +0.2°; +0.7°; −0.5°; −3.0°). More successful examples of preferential crystallization of one enantiomer appeared in the literature notably with tri-*o*-thymotide,[356] and 1,1′-binaphthyl.[357,358] In the latter case, the distribution of specific rotations recorded for several independent experiments is centred to zero.

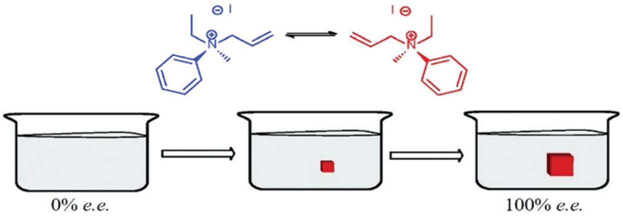

Fig. 13 Enantiomeric preferential crystallization of *N*,*N*,*N*-allylethylmethylanilinium iodide as described by Havinga. Fast racemization in solution supplies the growing crystal with the appropriate enantiomer. Adapted from ref. 55 with permission from the Royal Society of Chemistry, copyright 2015.

Sodium chlorate ($NaClO_3$) crystallizes by evaporation of water into a conglomerate ($P2_13$ space group).[359–361] Preferential crystallization of one of the crystal enantiomorph over the other was already reported by Kipping and Pope in 1898.[362,363] From static (*i.e.* non-stirred) solution, $NaClO_3$ crystallization seems to undergo an uncertain resolution, similar to Havinga's findings with the aforementioned quaternary ammonium salt. However, a statistically significant bias in favour of D-crystals was invariably observed, likely due to the presence of biocontaminants.[364] Interestingly, Kondepudi *et al.* showed in 1990 that magnetic stirring, during the crystallization of sodium chlorate, randomly oriented the crystallization to only one enantiomorph, with a virtually perfect bimodal distribution over several samples (±1).[365] Further studies[366–369] revealed that the maximum degree of supersaturation is solely reached once, when the first primary nucleation occurs. At this stage, the magnetic stirring bar breaks up the first nucleated crystal into small fragments that have the same chirality than the 'Eve crystal', and act as secondary nucleation centres whence crystals grow (Fig. 14). This constitutes a SMSB process coupling homochiral self-replication plus inhibition through the supersaturation drop during secondary nucleation, precluding new primary nucleation and the formation of crystals of the mirror-image form.[307] This deracemization strategy was also successfully applied to 4,4′-dimethyl-chalcone,[370] and 1,1′-binaphthyl (from its melt).[371]

In 2005, Viedma reported that solid-to-solid deracemization of $NaClO_3$ proceeded from its saturated solution by abrasive grinding with glass beads.[373] Complete homochirality with bimodal distribution is reached after several hours or days.[374] The process can also be triggered by replacing grinding with ultrasound,[375] turbulent flow,[376] or temperature variations.[376,377] Although this deracemization process is easy to implement, the mechanism by which SMSB emerges is an ongoing highly topical question that falls outside the scope of this review.[40,41,378–381]

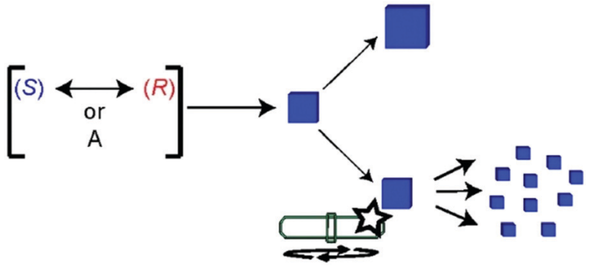

Fig. 14 Primary nucleation of an enantiopure 'Eve crystal' of random chirality, slightly amplified by growing under static conditions (top, Havinga-like), or strongly amplified by secondary nucleation thanks to magnetic stirring (bottom, Kondepudi-like) from rapidly racemizing chiral molecules, (*S*) and (*R*), or achiral molecules, A. Reprinted from ref. 55 with permission from the Royal Society of Chemistry, copyright 2015.

Viedma ripening was exploited for deracemization of conglomerate-forming achiral or chiral compounds (Fig. 15).[55,382] The latter can be formed *in situ* by a reaction involving a prochiral substrate. For example, Vlieg *et al.* coupled an attrition-enhanced deracemization process with a reversible organic reaction (an aza-Michael reaction) between prochiral substrates under achiral conditions to produce an enantiopure amine.[383] In a recent review, Buhse and co-workers identified a range of conglomerate-forming molecules that can be potentially deracemized by Viedma ripening.[41] Viedma ripening also proves to be successful with molecules crystallizing as racemic compounds under the condition that the conglomerate form is energetically accessible.[384] Furthermore, a promising mechanochemical method to transform racemic compounds of amino acids into their corresponding conglomerates has been recently found.[385] When valine, leucine and isoleucine were milled one hour in the solid state, in a Teflon jar with a zirconium ball and in the decisive presence of zinc oxide, their corresponding conglomerates eventually formed.

Shortly after the discovery of Viedma, aspartic acid[386] and glutamic acid[387,388] were deracemized up to the homochiral state starting from biased racemic mixtures. The chiral γ-polymorph of glycine[389] was obtained with a preferred handedness by Ostwald ripening, albeit with a stochastic distribution of the optical activities.[390] Salts or imine derivatives of alanine,[391,392] phenylglycine[372,384] and phenylalanine[391,393] were desymmetrized by Viedma ripening with DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) as the racemization catalyst. Successful deracemization was also achieved with amino acid precursors such as α-aminonitriles,[394–396] α-iminonitriles,[397] *N*-succinopyridine[398] and thiohydantoins.[399] The first three classes of compounds could be obtained directly from prochiral precursors by coupling synthetic reactions and Viedma ripening. In the preceding examples, the direction of the SMSB process is selected by biasing the initial racemic mixtures in favour of one enantiomer or by seeding the crystallization with chiral chemical additives. In the next sections, we will consider the possibility to drive the SMSB process towards a deterministic outcome by means of PVED, physical fields, polarized particles, and chiral surfaces, *i.e.* the sources of asymmetry depicted in Parts 2 and 3 of this review.

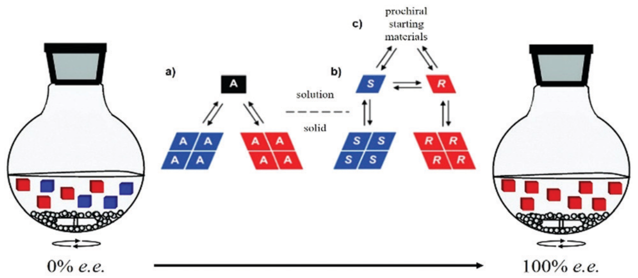

Fig. 15 Schematic representation of Viedma ripening and solution–solid equilibria of an intrinsically achiral molecule (a) and a chiral molecule undergoing solution-phase racemization (b). The racemic mixture can result from chemical reaction involving prochiral starting materials (c). Adapted from ref. 55 with permission from the Royal Society of Chemistry, copyright 2015 and from ref. 372. Copyright 2008. American Chemical Society.

### 4.3 Deterministic SMSB processes

**(a) Parity violation coupled to SMSB.** In the 1980s, Kondepudi and Nelson constructed stochastic models of a Frank-type autocatalytic network which allowed them to probe the sensitivity of the SMSB process to very weak chiral influences.[304,400–402] Their estimated energy values for biasing the SMSB process into a single direction was in the range of PVED values calculated for biomolecules. Despite the competition with the bias originated from random fluctuations (as underlined later by Lente),[126] it appears possible that such a very weak "asymmetric factor can drive the system to a preferred asymmetric state with high probability".[307] Recently, Blackmond and co-workers performed a series of experiments with the objective of determining the energy required for overcoming the stochastic behaviour of well-designed Soai[403] and Viedma ripening experiments.[404] This was done by performing the SMSB processes with very weak chiral inductors, isotopically chiral molecules and isotopologue enantiomers for the Soai reaction and the Viedma ripening, respectively. The calculated energies, 0.15 kJ $\text{mol}^{-1}$ (for Viedma) and $2 \times 10^{-8}$ kJ $\text{mol}^{-1}$ (for Soai), are considerably higher than the PVED estimates (*ca.* $10^{-12}$–$10^{-15}$ kJ $\text{mol}^{-1}$). This indicates that the two experimental SMSB processes reported to date are not sensitive enough to detect any influence of PVED and questions the existence of an ultra-sensitive auto-catalytic process, as the one described by Kondepudi and Nelson.

The possibility to bias crystallization processes with chiral particles emitted by radionuclides was probed by several groups as summarized in the reviews of Bonner.[44,54] Kondepudi-like crystallization of $NaClO_3$ in the presence of β particles from a ${}_{39}Sr^{90}$ source notably yielded a distribution of (+) and (−)-$NaClO_3$ crystals, largely biased in favour of (+) crystals.[405] It was presumed that spin polarized electrons produced chiral nucleating sites, albeit chiral contaminants cannot be excluded.

**(b) Chiral surfaces coupled to SMSB.** The extreme sensitivity of the Soai reaction to chiral perturbations is not restricted to soluble chiral species.[312] Enantio-enriched or enantiopure pyrimidine alcohol was generated with determined configuration when the auto-catalytic reaction was initiated with chiral crystals, such as (α)-quartz,[406] γ-glycine,[407] *N*-(2-thienylcarbonyl)glycine,[408] cinnabar,[409] anhydrous cytosine,[292] or triglycine sulfate,[410] or with enantiotopic faces of achiral crystals such as $CaSO_4 \cdot 2H_2O$ (gypsum).[411] Even though the selective adsorption of product to crystal faces has been observed experimentally[409] and computed,[408] the nature of the heterogeneous reaction steps that provide the initial enantiomer bias remains to be determined.[300]

The effect of chiral additives on crystallization processes, in which the additive inhibits one of the enantiomer growth thereby enriching the solid phase with the opposite enantiomer is well established as "the rule of reversal".[412,413] In the realm of the Viedma ripening, Noorduin *et al.* discovered in 2020 a way of propagating homochirality between α-iminonitriles, possible intermediates in the Strecker synthesis of α-amino acids.[414] These authors demonstrated that an enantiopure additive (1–20 mol%) induces an initial enantio-imbalance, which is then amplified by Viedma ripening up to a complete mirror-symmetry breaking. In contrast to the "rule of reversal", the additive favours the formation of the product with identical configuration. The additive is actually incorporated in a thermodynamically controlled way into the bulk crystal lattice of the crystallized product of the same configuration, *i.e.* a solid solution is formed enantiospecifically.

**(c) CPL coupled to SMSB.** Coupling CPL-induced enantioenrichment and amplification of chirality has been recognized as a valuable method to induce a preferred chirality to a range of assemblies and polymers.[182,183,354,415,416] On the contrary, the implementation of CPL as a trigger to direct auto-catalytic processes towards enantiopure small organic molecules has been scarcely investigated.

CPL was successfully used in the realm of the Soai reaction to direct its outcome, either by using a chiroptical switchable additive, or by asymmetric photolysis of a racemic substrate. In 2004, Soai *et al.* illuminated for 48 h a photoresolvable chiral olefin with l- or r-CPL, and mixed it with the reactants of the Soai reaction to afford (*S*)- or (*R*)-5-pyrimidyl alkanol, respectively, in e.e. higher than 90%.[417] In 2005, the photolyzate of a pyrimidyl alkanol racemate acted as an asymmetric catalyst for its own formation reaching e.e. greater than 99.5%.[418] The enantiomeric excess of the photolyzate was below the detection level of chiral HPLC instrument but was amplified thanks to the SMSB process.

In 2009, Vlieg *et al.* coupled CPL with Viedma ripening to achieve complete and deterministic mirror-symmetry breaking.[419] Previous investigation revealed that the deracemization by attrition of the Schiff base of phenylglycine amide (***rac*-1**, Fig. 16a) always occurred in the same direction, the (*R*)-enantiomer, as a probable result of minute levels of chiral impurities.[372] CPL was envisaged as a potent chiral physical field to overcome this chiral interference. Irradiation of solid–liquid mixtures of ***rac*-1** indeed led to complete deracemization, the direction of which was directly correlated to the circular polarization of light. Control experiments indicated that the direction of the SMSB process is controlled by a non-identified chiral photoproduct generated upon irradiation of (***rac***)**-1** by CPL. This photoproduct (*S** or *R** in Fig. 16b) then serves as an enantioselective crystal-growth inhibitor which mediates the deracemization process towards the other enantiomer (Fig. 16b). In the context of BH, this work highlights that asymmetric photosynthesis by CPL is a potent mechanism that can be exploited to direct deracemization processes when coupled to an amplification phenomenon.

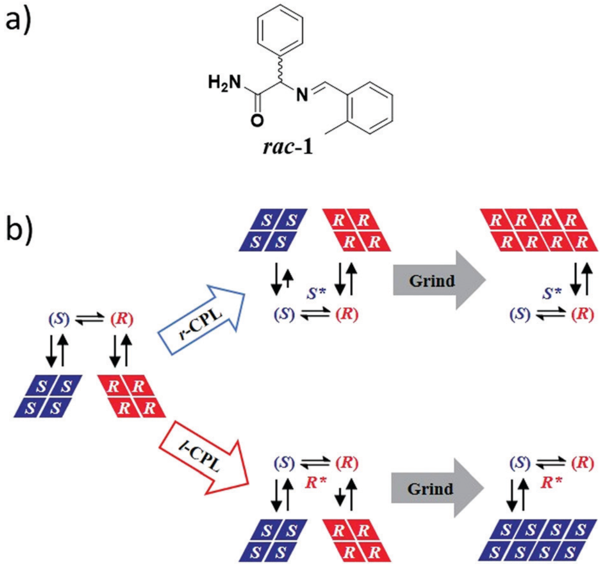

Fig. 16 (a) Molecular structure of ***rac*-1**. (b) CPL-controlled complete attrition-enhanced deracemization of ***rac*-1**. (*S*) and (*R*) are the enantiomers of ***rac*-1** and *S** and *R** are chiral photoproducts formed upon CPL irradiation of ***rac*-1**.[419]

## 5. Theories for the emergence of BH

Physical fields, CPL, polarized particles, polarized spins, chiral surfaces and SMSB processes have been presented as potential candidates for the emergence of chiral biases in prebiotic molecules. Their main properties are summarized in Table 1. The plausibility of the occurrence of these biases under the conditions of the primordial universe has also been evoked for certain physical fields (such as CPL or CISS). However, it is important to provide a more global overview of the current theories that tentatively explain the following puzzling questions: where, when and how did the molecules of life reach a homochiral state? At which point of this undoubtedly intricate process did life emerge?

### 5.1 Terrestrial or extra-terrestrial origin of BH?

The enigma of the emergence of BH might potentially be solved by finding the location of the initial chiral bias, might it be on earth or elsewhere in the universe. The 'panspermia' hypothesis,[424] according to which living organisms were transplanted to earth from another solar system, sparked interest on the extra-terrestrial origin of BH, but the fact that such a high level of chemical and biological evolution was present on

**Table 1** Potential sources of asymmetry and "by chance" mechanisms for the emergence of a chiral bias in prebiotic and biologically-relevant molecules

| Type | Truly/ falsely chiral | Direction | Extent of induction | Scope | Relevance to BH | Selected references |
|---|---|---|---|---|---|---|
| PV | Truly | Unidirectional, deterministic, (+) or (−) for a given molecule | Minute[a] | Any chiral molecules | PVED: theo. calculations (natural) polarized particles: asymmetric destruction of racemates[b] | 44, 53 and 54 |
| MChD | Truly | Bidirectional, (+) or (−) depending on the relative orientation of light and magnetic field | Minute[c] | Chiral molecules with high $g_{NCD}$ and $g_{MCD}$ values | Proceed with unpolarised light | 137 |
| Aligned magnetic field, gravity and rotation | Falsely | Bidirectional, (+) or (−) depending on the relative orientation of angular momentum and effective gravity | Minute[d] | Large supramolecular aggregates | Ubiquitous natural physical fields | 161 |
| Vortices | Truly | Bidirectional, (+) or (−) depending on the direction of the vortices | Minute[d] | Large objects or aggregates | Ubiquitous natural physical field (pot, present in hydrothermal vents) | 151 and 160 |
| CPL | Truly | Bidirectional, (+) or (−) depending on the direction of CPL | Low to Moderate[e] | Chiral molecules with high $g_{NCD}$ values | Asymmetric destruction of racemates | 58 |
| Spin-polarized electrons (CISS effect) | Truly | Bidirectional, (+) or (−) depending on polarization | Low to high[f] | Any chiral molecules | Enantioselective adsorption/ crystallization of racemate, asymmetric synthesis | 233 |
| Chiral surfaces | Truly | Bidirectional, (+) or (−) depending on surface chirality | Low to excellent | Any adsorbed chiral molecules | Enantioselective adsorption of racemates | 238 and 244 |
| SMSB (crystallization) | na | Bidirectional, stochastic distribution of (+) or (−) for repeated processes | Low to excellent | Conglomerate-forming molecules | Resolution of racemates | 55 and 382 |
| SMSB (asymmetric auto-catalysis) | na | Bidirectional, stochastic distribution of (+) or (−) for repeated processes | Low to excellent | Soai reaction | To be demonstrated | 312 |
| Chance mechanisms | na | Bidirectional, stochastic distribution of (+) or (−) for repeated processes | Minute[g] | Any chiral molecules | To be demonstrated | 17 and 420–422 |

[a] PVED $\approx 10^{-12}$–$10^{-15}$ kJ $mol^{-1}$.[53] [b] However, experimental results are not conclusive (see Part 3.2(b)). [c] e.e.$_{MChD} = g_{MChD}/2$ with $g_{MChD} \approx (g_{NCD} \times g_{MCD})/2$. NCD: natural circular dichroism. MCD: magnetic circular dichroism. For the resolution of Cr complexes,[137] e.e. = $k \times B$ with $k = 10^{-5}$ $T^{-1}$ at $\lambda = 695.5$ nm. [d] The minute chiral induction is amplified upon aggregation leading to homochiral helical assemblies.[423] [e] For photolysis, e.e. depends both on $g$ and the extent of reaction (see eqn (2) and the text in part 3.2(a)). Up to a few e.e. percent have been observed experimentally.[197–199] [f] Recently, spin-polarized SE through the CISS effect have been implemented as chiral reagents with relatively high e.e. values (up to a ten percent) reached for a set of reactions.[236] [g] The standard deviation for 1 mole of chiral molecules is of $1.9 \times 10^{11}$.[126]na: not applicable.

celestial objects has not been supported by any scientific evidence.[44] Accordingly, terrestrial and extra-terrestrial scenarios for the original chiral bias in prebiotic molecules will be considered in the following.

**(a) Terrestrial origin of BH.** A range of chiral influences have been evoked for the induction of a deterministic bias to primordial molecules generated on earth. Enantiospecific adsorptions or asymmetric syntheses on the surface of abundant minerals have long been debated in the context of BH[44,238–242] since no significant bias of one enantiomorphic crystal or surface over the other has been measured when counting is averaged over several locations on earth.[257,258] Prior calculations supporting PVED at the origin of excess of L-quartz over D-quartz[114,425] or favouring the A-form of kaolinite[426] are thus contradicted by these observations. Abyssal hydrothermal vents during the Hadean/Eo-Archaean eon are argued as the most plausible regions for the formation of primordial organic molecules on the early earth.[427] Temperature gradients may have offered the different conditions for the coupled autocatalytic reactions and clays may have acted as catalytic sites.[347] However, chiral inductors in these geochemically reactive habitats are hypothetical, even though vortices[60] or CISS occurring at the surfaces of greigite has been mentioned recently.[428] CPL and MChD are not potent asymmetric forces on earth as a result of low levels of circular polarization detected for the former and small anisotropic factors of the latter.[429–431] PVED is an appealing ''intrinsic'' chiral polarization of matter but its implication in the emergence of BH is questionable (Part 2).[126]

Alternatively, theories suggesting that BH emerged from scratch, *i.e.* without any involvement of the chiral discriminating sources mentioned in Part 2–3 and SMSB processes (Part 4), have been mentioned in the literature for a long time,[420] and variant versions appeared sporadically. Herein, these mechanisms are named ''random'' or ''by chance'' and are based on probabilistic grounds only (Table 1). The prevalent form comes from the fact that a racemate is very unlikely made of exactly equal amounts of enantiomers, due to natural fluctuations described statistically like coin tossing.[126,432] One mole of chiral molecules actually exhibits a standard deviation of $1.9 \times 10^{11}$. Putting into relation this statistical variation and putative strong chiral amplification mechanisms and evolutionary pressures, Siegel suggested that homochirality is an imperative of molecular evolution.[17] However, the probability to get both homochirality and life emerging from statistical fluctuations at the molecular scale appears very unlikely.[35,59,433] SMSB phenomena may amplify statistical fluctuations up to the homochiral state, yet the direction of process for multiple occurrences will be left to chance in the absence of a chiral inducer (Part 4). Other theories suggested that homochirality emerges during the formation of biopolymers ''by chance'', as a consequence of the limited number of sequences that can be possibly contained in a reasonable amount of macromolecules (see Part 5.3).[17,421,422] Finally, kinetic processes have also been mentioned in which a given chemical event would have occurred to a larger extent for one enantiomer over the other under achiral conditions (see one possible physicochemical scenario in Fig. 11). Hazen notably argued that nucleation processes governing auto-catalytic events occurring at the surface of crystals are rare and thus a kinetic bias can emerge from an initially unbiased set of prebiotic racemic molecules.[239] Random and by chance scenarios towards BH might be attractive on a conceptual view but lack experimental evidence.

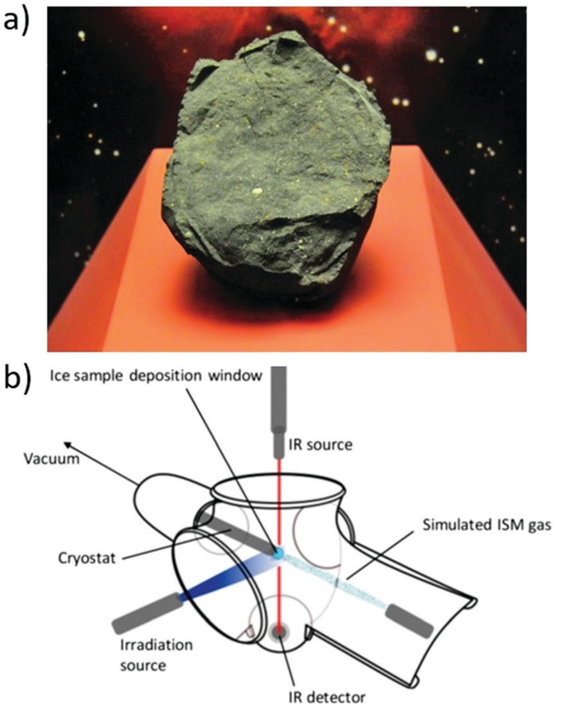

Fig. 17 (a) A fragment of a meteorite landed in Murchison, Australia, in 1969, exhibited at the National Museum of Natural History (Washington). (b) Scheme of the preparation of interstellar ice analogues. A mixture of primitive gas molecules is deposited and irradiated under vacuum on a cooled window. Composition and thickness are monitored by infrared spectroscopy. Reprinted from ref. 434 with permission from MDPI. Copyright 2019. Licensee MDPI under Creative Commons Attribution 4.0 International License https://creativecommons.org/licenses/by/4.0/.

**(b) Extra-terrestrial origin of BH.** Scenarios suggesting a terrestrial origin behind the original enantiomeric imbalance leave a question unanswered: how an earth-based mechanism can explain enantioenrichment in extra-terrestrial samples?[59,433] However, to stray from ''geocentrism'' is still worthwhile; another plausible scenario is the exogenous delivery on earth of enantioenriched molecules relevant for the appearance of life. The body of evidence grew from the characterization of organic molecules, especially amino acids and sugars, and their respective optical purity, in meteorites,[59] comets, and laboratory-simulated interstellar ices.[434]

The 100 kg Murchison's meteorite that fell at Australia in 1969 is generally considered as the standard reference for extraterrestrial organic matter (Fig. 17a).[435] In fifty years, the analyses of its composition revealed more than ninety α, β, γ and δ-isomers of $C_2$ to $C_9$ amino acids, diamino acids, and dicarboxylic acids as well as numerous polyols including sugars (ribose,[436] a building block of RNA), sugar acids and alcohols, but also α-hydroxycarboxylic acids[437] and deoxy acids.[434]

Unequal amounts of enantiomers were also found with a quasi-exclusive predominance for (*S*)-amino acids[57,285,438–440] ranging from 0 to 26.3 ± 0.8% e.e. values (highest e.e. being measured for non-proteinogenic α-methyl amino acids),[441] and, when they are not racemates, only D-sugar acids with an e.e. of up to 82% for xylonic acid have been detected.[442] These measurements are relatively scarce for sugars and in general need to be repeated, notably to definitely exclude their potential contamination by terrestrial environment. Future space missions to asteroids, comets and Mars, coupled with more advanced analytical techniques,[443] will indubitably lead to a better determination of the composition of extra-terrestrial organic matter. The fact that major enantiomers of extra-terrestrial amino acids and sugar derivatives have the same configuration as the building blocks of life constitutes a promising set of results.

To complete these analyses of the difficult-to-access outer space, laboratory experiments have been conducted by reproducing the plausible physicochemical conditions present on astrophysical ices (Fig. 17b).[444] Natural ones are formed in interstellar clouds,[445,446] on the surface of dust grains from which condensates a gaseous mixture of carbon, nitrogen and oxygen-based molecules (*e.g.* $H_2O$, $CH_3OH$, $CH_4$, $NH_3$, and $CO_2$),[447] under the influence of very low temperature (5–15 K)[448] and pressure. Subsequent photochemical processes in this mantle of frost are assumed to lead to complex molecules.[449] Since collapsing clouds gave birth to our solar system through the aggregation of dust grains,[450] studies of their composition receive a keen interest to broaden our knowledge about the prebiotic environment. Experiments on simulated interstellar ices support the formation of many proteinaceous amino acids,[451,452] and building blocks of RNA and DNA such as sugars,[453] like ribose[454] and deoxyribose,[455] as well as nucleobases (adenine, cytosine, uracil and thymine for example).[456] These molecules were obtained with no significant bias from the ideal racemic composition which supports their abiotic origin.[444] However, when similar experiments are conducted under CPL irradiation, amino acids are generated with significant biases towards one enantiomer as described in Part 3.2(a).[204,205]

The occurrence of CPL-driven photochirogenesis on interstellar dust grains was supported by the detection of near-infrared light with significant circular polarization degrees (up to 22%),[457] in parsec-sized star-forming regions, such as massive molecular clouds.[458–464] Cosmic circularly polarized photons arise from synchrotron radiations emitted by neutron stars, remnants of supernovae explosions,[35] through bremsstrahlung, dichroic scattering and/or light extinction (along lined up grains).[465] In addition, although it was not directly observed due to dust shielding, models predicted the generation of vacuum ultraviolet (VUV) and UV-CPL under these conditions,[459] *i.e.* spectral regions of light absorbed by amino acids and sugars. Photolysis by broad band and optically impure CPL is expected to yield lower enantioenrichments than those obtained experimentally by monochromatic and quasi-perfect circularly polarized synchrotron radiation (see Part 3.2a).[198] However, a broad band CPL is still capable of inducing chiral bias by photolysis of an initially abiotic racemic mixture of aliphatic α-amino acids as previously debated.[466,467] Likewise, CPL in the UV range will produce a wide range of amino acids with a bias towards the (*S*) enantiomer,[195] including α,α-dialkyl amino acids.[468]

l- and r-CPL produced by a neutron star are equally emitted in vast conical domains in the space above and below its equator.[35] However, appealing hypotheses were formulated against the apparent contradiction that amino acids have always been found as predominantly (*S*) on several celestial bodies,[59] and the fact that CPL is expected to be portioned into left- and right-handed contributions in equal abundance within the outer space. In the 1980s, Bonner and Rubenstein proposed a detailed scenario in which the solar system, revolving around the centre of our galaxy, had repeatedly traversed a molecular cloud and accumulated enantio-enriched incoming grains.[430,469] The same authors assumed that this enantioenrichment would come from asymmetric photolysis induced by synchrotron CPL emitted by a neutron star at the stage of planet formation. Later, Meierhenrich remarked in addition that, in molecular clouds, regions of homogeneous CPL polarization can exceed the expected size of a protostellar disk – or of our solar system,[458,470] allowing a unidirectional enantioenrichment within our solar system, including comets.[24] A solid scenario towards BH thus involves CPL as a source of chiral induction for biorelevant candidates, through photochemical processes on the surface of dust grains, and delivery of the enantio-enriched compounds on primitive earth by direct grain accretion or by impact[471] of larger objects (Fig. 18).[472–474]

The high enantiomeric excesses detected for (*S*)-isovaline in certain stones of the Murchison's meteorite (up to 15.2 ± 0.2%) suggested that CPL alone cannot be at the origin of this enantioenrichment.[285] The broad distribution of e.e. values (0–15.2%) and the abundance ratios of isovaline relatively to other amino acids also point to (*S*)-isovaline (and probably other amino acids) being formed through multiple synthetic processes that occurred during the chemical evolution of the meteorite.[440] Finally, based on the anisotropic spectra,[188] it is highly plausible that other physiochemical processes, *e.g.* racemization coupled to phase transitions or coupled non-equilibrium/equilibrium processes,[378,475] have led to a change in the ratio of enantiomers initially generated by UV-CPL.[59] In addition, a serious limitation of the CPL-based scenario shown in Fig. 18 is that significant enantiomeric excesses can only be reached at high conversion, *i.e.* by decomposition of most of the organic matter (see eqn (2) in Part 3.2(a)). Even though there is a solid foundation for CPL being involved as an initial inducer of chiral bias in extra-terrestrial organic molecules, chiral influences other than CPL cannot be excluded. Induction and enhancement of optical purities by physicochemical processes occurring at the surface of meteorites and potentially involving water and the lithic environment have been evoked but have not been assessed experimentally.[285]

Asymmetric photoreactions[431] induced by MChD can also be envisaged notably in a neutron star environment, of tremendous magnetic fields ($10^8$–$10^{12}$ T) and synchrotron radiations.[35,476] Spin-polarized electrons (SPEs), another potential source of

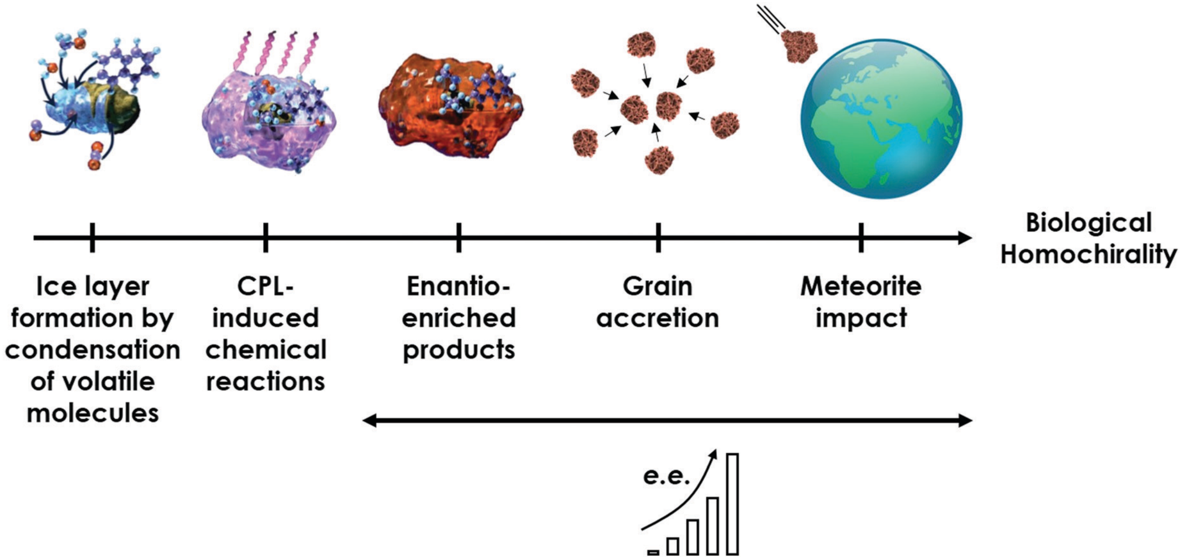

Fig. 18 CPL-based scenario for the emergence of BH following the seeding of the early earth with extra-terrestrial enantio-enriched organic molecules. Adapted from ref. 474 with permission from Wiley-VCH, copyright 2015.

asymmetry, can potentially be produced upon ionizing irradiation of ferrous magnetic domains present in interstellar dust particles, aligned by enormous magnetic fields produced by a neutron star. One enantiomer from a racemate in a cosmic cloud could adsorb enantiospecifically on the magnetized dust particle. In addition, meteorites contain magnetic metallic centres that can act as asymmetric reaction sites upon generation of SPEs. Finally, polarized particles such as antineutrinos (the SNAAP model[226–228]) have been proposed as a deterministic source of asymmetry, at work in the outer space. Radioracemization must potentially be considered as a jeopardizing factor in that specific context.[44,477,478] Further experiments are needed to probe whether these chiral influences have played a role in the generation of the enantiomeric imbalances detected in celestial bodies.

### 5.2 Purely abiotic scenarios

Emergence of life and biomolecular homochirality must be tightly linked,[46,479,480] but in such a way that needs to be cleared up. As recalled recently by Glavin, homochirality by itself cannot be considered as a biosignature.[59] Non proteinogenic amino acids are predominantly (*S*) and abiotic physicochemical processes can lead to enantio-enriched molecules. However, it has been widely substantiated that polymers of life (proteins, DNA, and RNA) as well as lipids need to be enantiopure to be functional. Considering the NASA definition of life, ''a self-sustaining chemical system capable of Darwinian evolution'',[481] and the ''widespread presence of ribonucleic acid (RNA) cofactors and catalysts in today's terran biosphere'',[482] a strong hypothesis for the origin of Darwinian evolution and life is ''the abiotic formation of long-chained RNA polymers'' with the ability to self-replicate.[309] Current theories differ by placing the emergence of homochirality at different times of the chemical and biological evolutions leading to life. Regarding on whether homochirality happens before or after the appearance of life discriminates between purely abiotic and biotic theories, respectively (Fig. 19). In between these two extreme cases, homochirality could have emerged during the formation of primordial polymers and/or their evolution towards more elaborated macromolecules.

(a) **Enantiomeric cross-inhibition.** The puzzling question regarding primeval functional polymers is whether they form from enantiopure, enantio-enriched, racemic or achiral building blocks. A theory that has found great support in the chemical community is that homochirality was already present at the stage of the primordial soup, *i.e.* the building blocks of life were enantiopure. Proponents of the purely abiotic origin of homochirality mostly refer to the inefficiency of polymerization reactions when conducted from mixtures of enantiomers. More precisely, the term enantiomeric cross-inhibition was coined to describe experiments for which the rate of the polymerization reaction and/or the length of the polymers were significantly reduced when non-enantiopure mixtures were used instead of enantiopure ones.[24,44] Seminal studies were conducted by oligo- or polymerizing α-amino acid *N*-carboxy-anhydrides (NCAs) in the presence of various initiators. Idelson and Blout observed in 1958 that (*R*)-glutamate-NCA added to the reaction mixture of (*S*)-glutamate-NCA led to a significant shortening of the resulting polypeptides, inferring that (*R*)-glutamate provoked the chain termination of (*S*)-glutamate oligomers.[483] Lundberg and Doty also observed that the rate of polymerization of (*R*)/(*S*) mixtures of a glutamate-NCA and the mean chain length reached at the end of the polymerization were decreased relative to those of pure (*R*)- or (*S*)-glutamate-NCA.[485,486] Similar studies for oligonucleotides were performed with an enantiopure template to replicate activated complementary nucleotides. Joyce *et al.* showed in 1984 that guanosine oligomerization, directed by a poly-D-cytosine template, was inhibited when conducted with a

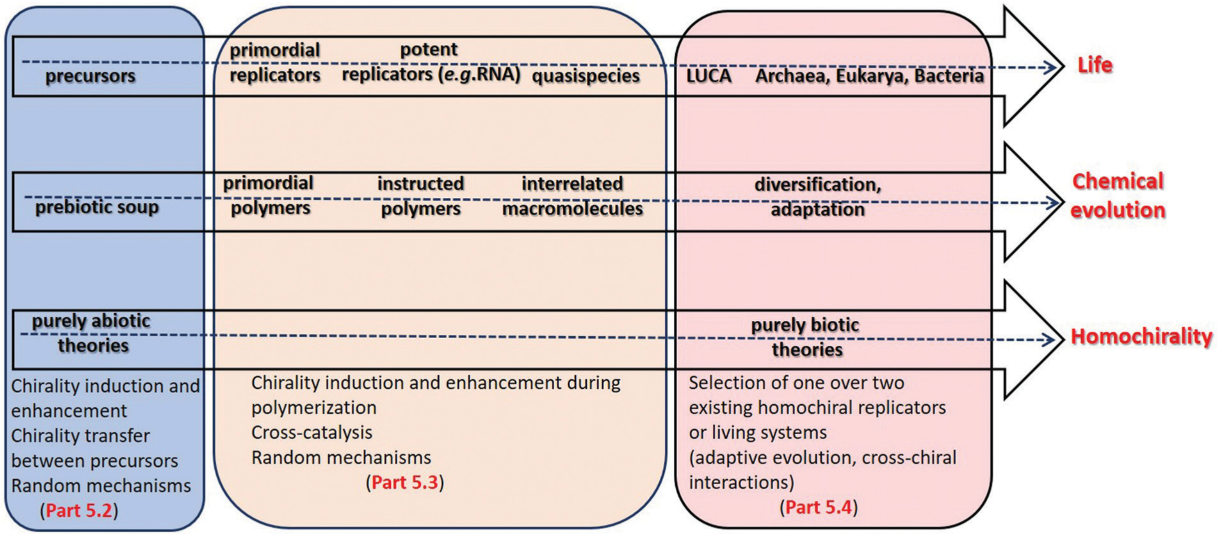

Fig. 19 Possible connections between the emergences of life and homochirality at the different stages of the chemical and biological evolutions. Possible mechanisms leading to homochirality are indicated below each of the three main scenarios. Some of these mechanisms imply an initial chiral bias which can be of terrestrial or extra-terrestrial origins as discussed in Part 5.1. LUCA = Last Universal Cellular Ancestor.

racemic mixture of activated mononucleotides.[484] The L residues are predominantly located at the chain-end of the oligomers, acting as chain terminators, thus decreasing the yield of oligo-D-guanosine. A similar conclusion was reached by Goldanskii and Kuz'min upon studying the dependence of the length of enantiopure oligonucleotides on the chiral composition of the reactive monomers.[429] Interpolation of their experimental results with a mathematical model led to the conclusion that the length of potent replicators will dramatically be reduced in the presence of enantiomeric mixtures reaching a value of 10 monomer units at best for a racemic medium.

Finally, the oligomerization of activated racemic guanosine was also inhibited on DNA and PNA templates.[487] The latter being achiral, it suggests that enantiomeric cross-inhibition is intrinsic to the templated oligomerization process involving complementary nucleobases.

**(b) Propagation and enhancement of the primeval chiral bias.** Studies demonstrating enantiomeric cross-inhibition during polymerization reactions have led the proponents of purely abiotic origin of BH to propose several scenarios for the formation of building blocks of life in an enantiopure form. In this regard, racemization appears as a redoubtable opponent considering that harsh conditions – intense volcanism, asteroid bombardment and scorching heat[488,489] – prevailed between earth formation, 4.5 billion years ago, and the appearance of life, 3.5 billion years ago at the latest.[490,491] At that time, deracemization inevitably suffered from its nemesis, racemization, which may take place in days or less in a hot alkaline aqueous medium.[35,301,492–494]

Several scenarios have considered that initial enantiomeric imbalances have probably been decreased by racemization but not eliminated. Abiotic theories thus rely on processes that would be able to amplify tiny enantiomeric excesses (likely ≪ 1% e.e.) up to the homochiral state. Intermolecular interactions cause enantiomer and racemate to have different physicochemical properties and this can be exploited to enrich a scalemic material into one enantiomer under strictly achiral conditions. This phenomenon of self-disproportionation of the enantiomers (SDE) is not rare for organic molecules and may occur through a wide range of physicochemical processes.[61] SDE with molecules of life such as amino acids and sugars is often discussed in the framework of the emergence of BH. SDE often occurs during crystallization as a consequence of the difference in solubility between racemic and enantiopure crystals, and its implementation to amino acids was exemplified by Morowitz as early as 1969.[495] It was confirmed later that a number of amino acids display high eutectic e.e. values which allows very high e.e. values to be present in solution, even from moderately biased enantiomeric mixtures.[496] Serine is the most striking example since a virtually enantiopure solution (>99% e.e.) is obtained at 25 °C under solid–liquid equilibrium conditions starting from a 1% e.e. mixture only.[497] Enantioenrichment was also reported for various amino acids after consecutive evaporations of their aqueous solutions[498] or preferential kinetic dissolution of their enantiopure crystals.[499] Interestingly, the eutectic e.e. values can be increased for certain amino acids by the addition of simple achiral molecules such as carboxylic acids.[500] DL-Cytidine, DL-adenosine and DL-uridine also form racemic crystals and their scalemic mixture can thus be enriched towards the D enantiomer in the same way provided t that the solution is saturated in both D and DL sugars.[501] SDE of amino acids does not occur solely during crystallization;[502] *e.g.* sublimation of near-racemic samples of serine yields a sublimate which is highly enriched in the major enantiomer.[503] Amplification of e.e. by sublimation has also been reported for other scalemic mixtures of amino acids,[504–506] or for a racemate mixed with a non-volatile optically pure amino acid.[507] Alternatively, amino acids were enantio-enriched by simple dissolution/precipitation of their phosphorylated derivatives in water.[508]

It is likely that prebiotic chemistry has linked amino acids, sugars and lipids in a way that remains to be determined. Merging the organocatalytic properties of amino acids with the aforementioned SDE phenomenon offers a pathway towards enantiopure sugars.[509] The aldol reaction between 2-chlorobenzaldehyde and acetone was found to exhibit a strongly positive non-linear effect, *i.e.* the e.e. in the aldol product is drastically higher than that expected from the optical purity of the engaged amino acid catalyst.[497] Again, the effect was particularly strong with serine since nearly racemic serine (1% e.e.) and enantiopure serine provided the aldol product with the same enantioselectivity (*ca.* 43% e.e., Fig. 20, (1)). Enamine catalysis in water was employed to prepare glyceraldehyde, the probable synthon towards ribose and other sugars, by reacting glycolaldehyde and formaldehyde in the presence of various enantiopure amino acids. It was found that all (*S*)-amino acids, except (*S*)-proline, provided glyceraldehyde with a predominant *R* configuration (up to 20% *e.e.* with (*S*)-glutamic acid, Fig. 20, (2)).[65,510] This result coupled to SDE furnished a small fraction of glyceraldehyde with 84% e.e. Enantio-enriched tetrose and pentose sugars are also produced by means of aldol reactions catalysed by amino acids and peptides in aqueous buffer solutions, albeit in modest yields.[511–513]

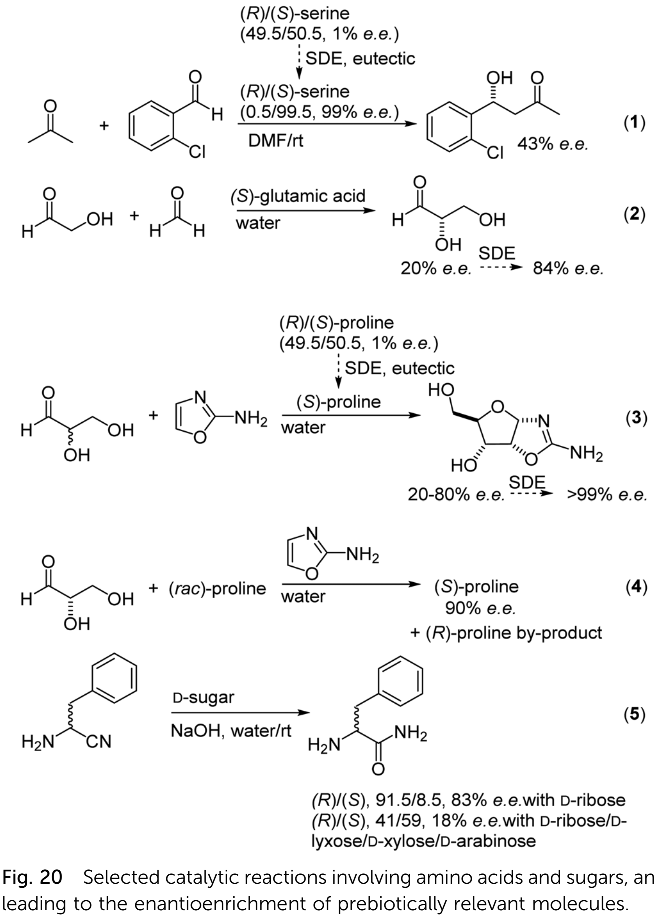

Fig. 20 Selected catalytic reactions involving amino acids and sugars, and leading to the enantioenrichment of prebiotically relevant molecules.

The influence of α-amino acids on the synthesis of RNA precursors was also probed. Along this line, Blackmond and co-workers reported that ribo- and arabino-amino oxazolines were enantio-enriched towards the expected D configuration when 2-aminooxazole and (*RS*)-glyceraldehyde were reacted in the presence of (*S*)-proline (Fig. 20, (3)).[514] When coupled with the SDE of the reacting proline (1% e.e.) and of the enantio-enriched product (20–80% e.e.), the reaction yielded enantiopure crystals of ribo-amino-oxazoline. (*S*)-Proline does not act as a mere catalyst in this reaction but rather traps the (*S*)-enantiomer of glyceraldehyde, thus accomplishing a formal resolution of the racemic starting material. The latter reaction can also be exploited in the opposite way to resolve a racemic mixture of proline in the presence of enantiopure glyceraldehyde (Fig. 20, (4)). This dual substrate/reactant behaviour motivated the same group to test the possibility of synthetizing enantio-enriched amino acids with D-sugars. The hydrolysis of 2-benzyl α-amino nitrile yielded the corresponding α-amino amide (precursor of phenylalanine) with various e.e. values and configurations depending on the nature of the sugars.[515] Notably, D-ribose provided the product with 70% e.e. biased in favour of unnatural (*R*)-configuration (Fig. 20, (5)). This result, which is apparently contradictory with such process being involved in the primordial synthesis of amino acids, was solved by finding that the mixture of four D-pentoses actually favoured the natural (*S*) amino acid precursor. This result suggests an unanticipated role of prebiotically relevant pentoses such as D-lyxose in mediating the emergence of amino acid mixtures with a biased (*S*) configuration.

How the building blocks of proteins, nucleic acids and lipids would have interacted between each other before the emergence of life is a subject of intense debate. The aforementioned examples in which prebiotic amino acids, sugars, and nucleotides would have mutually triggered their formation are actually not the privileged scenario of 'origin of life' practitioners. Most theories infer relationship at a more advanced stage of the chemical evolution. In the ''RNA world'',[516] a primordial RNA replicator catalysed the formation of the first peptides and proteins. Alternative hypotheses are that proteins (''metabolism first'' theory) or lipids[517] originated first[518] or that RNA, DNA and proteins emerged simultaneously by continuous and reciprocal interactions, *i.e.* mutualism.[519,520] It is commonly considered that homochirality would have arisen through stereoselective interactions between the different types of biomolecules, *i.e.* chirally matched combinations would have conducted to potent living systems whilst the chirally mismatched combinations would have declined. Such theory has notably been proposed recently to explain the splitting of lipids into opposite configurations in archaea and bacteria (known as the 'lipide divide')[521] and their persistence.[522] However, these theories do not address the fundamental question of the initial chiral bias and its enhancement.

SDE appears as a potent way to increase the optical purity of some building blocks of life but its limited scope, efficiency (an initial bias ≥1% e.e. is required) and productivity (high optical purity is reached at the cost of the mass of the material) appear detrimental for explaining the emergence of chemical homochirality. An additional drawback of SDE is that the enantioenrichment is only local, *i.e.* the overall material remains unenriched. SMSB processes as those mentioned in Part 4 are consequently considered as more probable alternatives towards homochiral prebiotic molecules. They disclose two major advantages: (i) a tiny fluctuation around the racemic state might be amplified up to the homochiral state in a deterministic manner, (ii) the amount of prebiotic molecules generated throughout these processes is potentially very high (*e.g.* in Viedma-type ripening experiments).[383] Even though experimental reports of SMSB processes have appeared in the literature for the last 25 years, none of them display conditions that appear relevant to prebiotic chemistry. The quest for small-molecule reactions, exhibiting asymmetric replication and persisting high selectivity, compatible with primeval conditions has recently been suggested as a key challenge for organic chemists.[523] Studying complex networks of organic chemical reactions[524] instead of single auto-catalytic events might shed light on cooperative systems from which homochirality might emerge.[302] In this context, open systems with a continuous supply of reactants are better suited to reach homochiral NESS and it is expected that current progresses made in studying the self-assembly process under dissipative conditions[525] will be extended to chiral reaction networks.[41]

### 5.3 Homochirality through polymerization

Purely abiotic theory is based on the argument that enantiomeric cross-inhibition will ineluctably impede the formation of potent replicators. However, the fact that chemical processes may follow dramatically different mechanisms depending on the conditions has been overlooked. Likewise, stereoselective and non-selective polymerization reactions which allow regular and random arrangements of the monomer enantiomers along the polymer backbone, respectively, are ubiquitous in polymer science, and cross-inhibition is likely to be the exception rather than the norm.[526,527]

**(a) Stereoselective polymerization or ligation.** Along this line, experimental efforts have been devoted to demonstrate the preferential formation of isotactic over heterochiral macromolecules for reactions initiated with racemic mixture of amino acids. An additional objective of these studies was to demonstrate the emergence of homochiral oligomers, of a sufficient size to sustain a secondary structure. It is indeed well established that the helical configuration present in peptides tends to improve further the stereoselectivity of the polymerization process, through preferential helical growth.[485,528] Goldberg studied the ligation of enantiopure amino esters, dipeptides and tripeptides (derived from alanine, aspartic acid and glycine) to racemic mixtures of activated alanine or aspartic acid amino esters in DMF and found a modest but significant bias towards the formation of homochiral peptides in the majority of cases.[529] More recent investigations by the group of Luisi on the polymerization of racemic α-amino acid NCAs of leucine (Leu), isoleucine (Ile), tryptophan (Trp) and glutamic acid (Glu) in buffered aqueous solution also indicated a slight bias towards homochiral sequences.[530] Excess factors, calculated relatively to a stereorandom polymerization process, were higher for the longer oligomers.[531] In the case of Leu, the presence of (α)-quartz as a 1 : 1 mixture of the D and L enantiomorphs was found to improve the stereoselectivity of the polymerization process thanks to the selective adsorption of the more regular homochiral peptides on the quartz surface.[532] The combination of (α)-quartz and a reaction mixture biased in favour of one of the amino-acid enantiomer (20% e.e.) was necessary to get homochiral sequences as the major component of the peptide stereoisomers.[533] The length of peptides reached under these conditions remains limited ($n < 10$) which lets the question of how long and well-structured homochiral peptides sequences emerged from the prebiotic soup unanswered. One possibility is that their formation was triggered by a ribozyme, *i.e.* that the construction of functional and catalytic RNAs preceded the generation of peptides and proteins.[516]

Synthetic chemistry aimed at mimicking prebiotic conditions for the synthesis of RNA oligomers has provided some support along this direction. Oligomers of up to 55 nucleotides can be synthetized by successive elongation of a decanucleotide with enantiopure nucleotides on $Na^+$-montmorillonite.[288] Subsequent experiments have then been conducted directly from racemic mixtures of activated mononucleotides in order to probe the possibility of generating homochiral RNA oligomers, again with $Na^+$-montmorillonite. Activated racemic adenosine oligomerized with comparable efficiency to enantiopure D-monomers discarding significant enantiomeric cross-inhibition.[534] The distribution of oligomer stereoisomers (up to 8 units under these conditions) appeared to be biased in favour of homochiral sequences. Deeper investigation of these reactions confirmed important and modest chiral selection in the oligomerization of activated adenosine[535–537] and uridine, respectively.[537] The co-oligomerization reaction of activated adenosine and uridine exhibited greater efficiency (up to 74% homochiral selectivity for the trimers) compared with the separate reactions of enantiomeric activated monomers.[538] Again, the length of oligomers detected in these experiments is far below the estimated number of nucleotides necessary to instigate chemical evolution.[540] This questions the plausibility of RNA as the primeval informational polymer. Joyce and co-workers evoked the possibility of a more flexible chiral polymer based on acyclic nucleoside analogues as an ancestor of the more rigid furanose-based replicators but this hypothesis has not been probed experimentally.[541]

Replication provided an advantage for achieving stereoselectivity provided that reactivity of chirally mismatched combinations are disfavoured relative to homochiral ones. A 32-residue peptide replicator was designed to probe the relationship between homochirality and self-replication.[539] Electrophilic and nucleophilic 16-residue peptide fragments of the same handedness were preferentially ligated, even in the presence of their enantiomers (*ca.* 70% of diastereomeric excess was reached when peptide fragments $E^L$, $E^D$, $N^E$, and $N^D$ were engaged, Fig. 21). The replicator entails a stereoselective autocatalytic cycle, for which all bimolecular steps are faster for

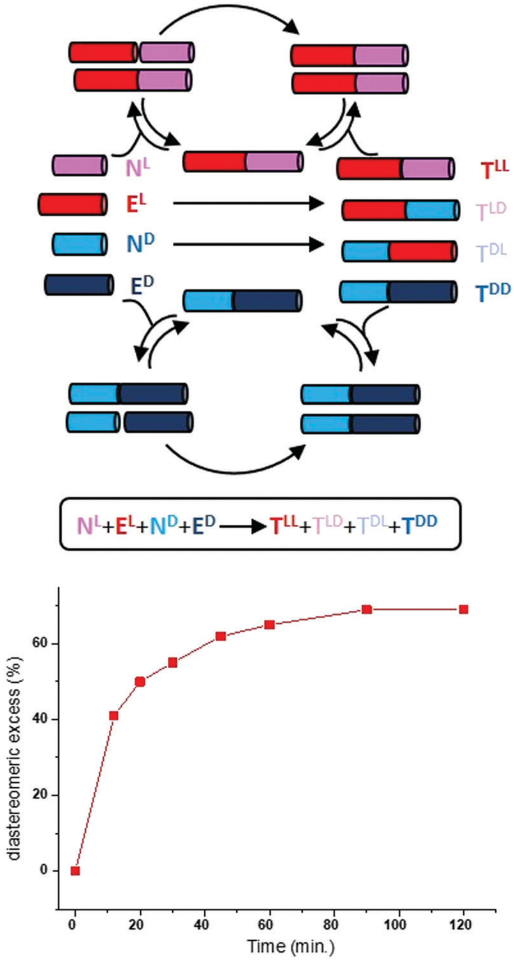

Fig. 21 Top: Schematic representation of the stereoselective replication of peptide residues with the same handedness. Below: Diastereomeric excess (*de*) as a function of time. de (%)= $[(T^{LL} + T^{DD}) - (T^{LD} + T^{DL})]/T^{total}$.[539]

matched *versus* unmatched pairs of substrate enantiomers, thanks to self-recognition driven by hydrophobic interactions.[542] The process is very sensitive to the optical purity of the substrates, fragments embedding a single (*S*)/(*R*) amino acid substitution lacked significant auto-catalytic properties. On the contrary, stereochemical mismatches were tolerated in the replicator; single mutated templates were able to couple homochiral fragments, a process referred to as ''dynamic stereochemical editing''.

Templating also appeared to be crucial for promoting the oligomerization of nucleotides in a stereoselective way. The complementarity between nucleobase pairs was exploited to achieve homochiral sequences of pyranosyl-RNA.[421] Activated homochiral tetramers containing hemi self-complementary base sequences (pr(GCCG)-2′3′cyclophosphate, pr = pyranosyl-ribo) yielded relatively long oligomers (a ten of units) under mild conditions. Heterochiral tetramers (*e.g.* DDDL, DDLD, and DLDD stereoisomers) were found to be poorly reactive under the same conditions. Importantly, the oligomerization of the homochiral tetramer was only slightly affected when conducted in the presence of heterochiral tetramers. These results raised the possibility that a similar experiment performed with the whole set of stereoisomers would have generated ''predominantly homochiral'' (L) and (D) sequence libraries of relatively long p-RNA oligomers. The studies with replicating peptides or auto-oligomerizing pyranosyl tetramers undoubtedly yield peptides and RNA oligomers that are both longer and optically purer than in the aforementioned reactions (Part 5.2) involving activated monomers. Further work is needed to delineate whether these elaborated molecular frameworks could have emerged from the prebiotic soup.

Replication in the aforementioned systems stems from the stereoselective non-covalent interactions established between products and substrates. Stereoselectivity in the aggregation of non-enantiopure chemical species is a key mechanism for the emergence of homochirality in the various states of matter.[543] The formation of homochiral *versus* heterochiral aggregates with different macroscopic properties led to enantioenrichment of scalemic mixtures through SDE as discussed in Part 5.2. Alternatively, homochiral aggregates might serve as templates at the nanoscale. In this context, the ability of serine (Ser) to preferentially form octamers when ionized from its enantiopure form is intriguing.[544] Moreover, (*S*)-Ser in these octamers can be substituted enantiospecifically by prebiotic molecules (notably D-sugars)[545] suggesting an important role of this amino acid in prebiotic chemistry. However, the preference for homochiral clusters is strong but not absolute and other clusters form when the ionization is conducted from racemic Ser,[546,547] making the implication of serine clusters in the emergence of homochiral polymers or aggregates doubtful.

Lahav and co-workers investigated in detail the correlation between aggregation and reactivity of amphiphilic activated racemic α-amino acids.[548] These authors found that the stereoselectivity of the oligomerization reaction is strongly enhanced under conditions for which β-sheet aggregates are initially present[549] or emerge during the reaction process.[550–552] These supramolecular aggregates serve as templates in the propagation step of chain elongation leading to long peptides and copeptides with a significant bias towards homochirality. Large enhancement of the homochiral content was detected, notably for the oligomerization of *rac*-Val NCA in the presence of 5% of an initiator (Fig. 22).[551] Racemic mixtures of isotactic peptides are desymmetrized by adding chiral initiators[551] or by biasing the initial enantiomer composition.[553,554] The interplay between aggregation and reactivity might have played a key role for the emergence of primeval replicators.

**(b) Heterochiral polymers.** DNA and RNA duplexes as well as protein secondary and tertiary structures are usually destabilized by incorporating chiral mismatches, *i.e.* by substituting the biological enantiomer by its antipode. As a consequence, heterochiral polymers, which can hardly be avoided from reactions initiated by racemic or quasi racemic mixtures of enantiomers, are mainly considered in the literature as hurdles for the emergence of biological systems. Several authors have nevertheless considered that these polymers could have formed at some point of the chemical evolution process towards potent

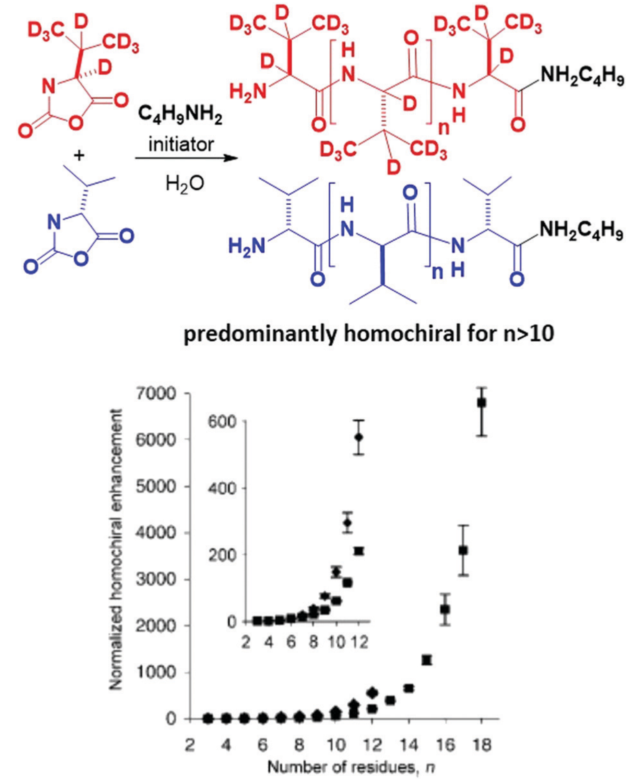

Fig. 22 Stereoselective polymerization of *rac*-Val *N*-carboxyanhydride in the presence of 5 mol% (square) or 25 mol% (diamond) of *n*-butylamine as the initiator. Homochiral enhancement is calculated relative to the binomial distribution of the stereoisomers. Reprinted from ref. 551 with permission from Wiley-VCH, copyright 2008.

biological polymers. This is notably based on the observation that the extent of destabilization of heterochiral *versus* homochiral macromolecules depends on a variety of factors, including the nature, number, location, and environment of the substitutions;[555] *e.g.* certain D to L mutations are tolerated in DNA duplexes.[556] Moreover, simulations recently suggested that "demi-chiral" proteins, which contain a 1 : 1 ratio of (*R*) and (*S*) α-amino acids, even though less stable than their homochiral analogues, exhibit structural requirements (folding, substrate binding and active sites) suitable for promoting early metabolism (*e.g.* t-RNA and DNA ligase activities).[557] Likewise, several racemic membranes, *i.e.* composed of lipid antipodes, were found to be of comparable stability to homochiral ones.[521]

Several scenarios towards BH involve non-homochiral polymers as possible intermediates towards potent replicators. Joyce proposed a three-phase process towards the formation of genetic materials assuming the formation of flexible polymers, constructed from achiral or prochiral acyclic nucleoside analogues, as intermediates towards RNA and finally DNA.[541] It was presumed that ribose-free monomers would be more easily accessed from the prebiotic soup than ribose ones and that the conformational flexibility of these polymers would work against enantiomeric cross-inhibition. Other simplified structures, relative to RNA, have been proposed by others.[558] However, the molecular structures of the proposed building blocks are still complex relative to what is expected to be readily generated from the prebiotic soup. Brewer and Davis hypothesized a set of more realistic polymers that could have emerged from very simple building blocks such as formaldehyde, α-substituted ketones, aldehydes, alkenes, amino-acids or α-hydroxy acids.[422] Polymers with random arrangement of (*R*) and (*S*) stereogenic centres are expected to be replicated through recognition of their chiral sequence. Such chiral encoding[559] might allow the emergence of replicators with specific catalytic properties. If one considers that the large number of possible sequences exceeds the number of molecules present in a reasonably sized sample of these chiral informational polymers, then their mixture will not constitute a perfect racemate since certain heterochiral polymers will lack their enantiomers. This argument of the emergence of homochirality or of a chiral bias "by chance" mechanism through the polymerization of a racemic mixture was also put forward previously by Eschenmoser[421] and Siegel.[17] This concept has been sporadically probed notably through the template-controlled copolymerization of the racemic mixtures of two different activated amino acids.[560–562] However, in the absence of any chiral bias, it is more likely that this mixture will yield informational polymers with pseudo enantiomeric like structures rather than the idealized chirally uniform polymers (see Part 5.4). Finally, the same authors also considered that pairing and replication between heterochiral polymers could operate through interaction between their helical structures, rather than on their individual stereogenic centres (Fig. 23).[422] On this specific point, it should be emphasized that the helical conformation adopted by the main chain of certain types of polymers can be "amplified", *i.e.* that single handed fragments may form even if composed of non-enantiopure building blocks.[563] For example, synthetic polymers embedding a modestly biased racemic mixture of enantiomers adopt a single-handed helical conformation thanks to the so-called "majority-rules" effect.[564–566] This phenomenon might have helped to enhance the helicity of the primeval heterochiral polymers relatively to the optical purity of their feeding monomers.

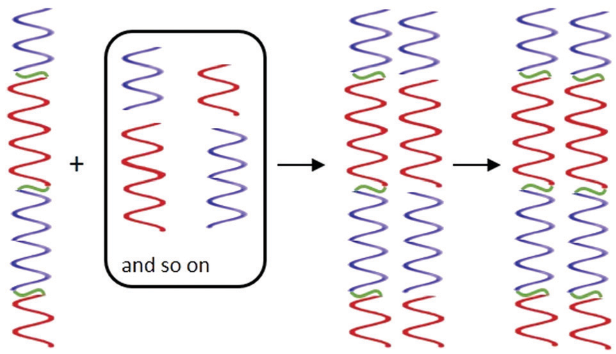

Fig. 23 Principle of chiral encoding in the case of a template consisting of regions of alternating helicity. The initially formed heterochiral polymer replicates by recognition and ligation of its constituting helical fragments.[422]

**(c) Theoretical models of polymerization.** Several theoretical models accounting for the homochiral polymerization of a molecule in the racemic state, *i.e.* mimicking a prebiotic stereoselective polymerization process, were developed by means of kinetic or probabilistic approaches. As early as 1966, Yamagata proposed that stereoselective polymerization coupled with different activation energies between reactive stereoisomers will "accumulate" the slight difference in energies between their composing enantiomers (assumed to originate from PVED) to eventually favour the formation of a single homochiral polymer.[108] Amongst other criticisms,[124] the unrealistic conditions of perfect stereoselectivity have been pointed out.[567] Yamagata later developed a probabilistic model which (i) favours ligations between monomers of the same chirality without discarding chirally mismatched combinations, (ii) gives an advantage of bonding between L monomers (again thanks to PVED) and (iii) allows racemization of the monomers and reversible polymerization. Homochirality in that case appears to develop much more slowly than the growth of polymers.[568] This conceptual approach neglects enantiomeric cross-inhibition and relies on the difference in reactivity between enantiomers which has not been observed experimentally. The kinetic model developed by Sandars[569] in 2003 received deeper attention as it revealed some intriguing features of homochiral polymerization processes. The model is based on the following specific elements: (i) chiral monomers are produced from an achiral substrate, (ii) cross-inhibition is assumed to stop polymerization, (iii) polymers of a certain length $N$ catalyse the formation of enantiomers in an enantiospecific fashion (similar to a nucleotide synthetase ribozyme), and (iv) the system is open, *i.e.* the achiral substrate is continously produced and polymers develop to a maximum length of $N$ units and then leave the system. By introducing a slight difference in the initial concentration values of the ($R$) and ($S$) enantiomers, bifurcation[304] readily occurs, *i.e.* polymers embedding a single enantiomer are formed. The required conditions are sufficiently high values of the kinetic constants associated with enantioselective production of the enantiomers and cross-inhibition.

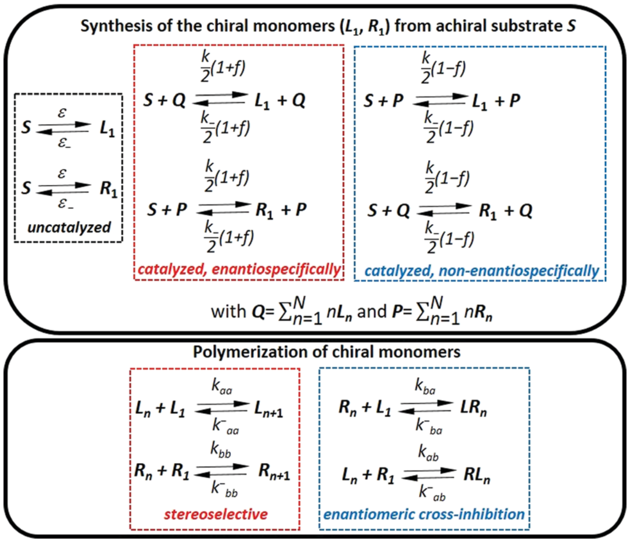

Fig. 24 The Hochberg model for chiral polymerization in closed systems. $N$ = maximum chain length of the polymer, $f$ = fidelity of the feedback mechanism, $Q$ and $P$ are the total concentrations of left-handed and right-handed polymers, respectively. $\varepsilon(\varepsilon_-)$, $k(k_-)$, $k_{aa}(k_{aa}^-)$, $k_{bb}(k_{bb}^-)$, $k_{ba}(k_{ba}^-)$, $k_{ab}(k_{ab}^-)$ denote the forward (reverse) reaction rate constants.[64]

The Sandars model was modified in different ways by several groups[570–574] to integrate more realistic parameters such as the possibility for polymers of all lengths to act catalytically in the breakdown of the achiral substrate into chiral monomers (instead of solely polymers of length $N$ as in the model of Sandars).[64,575] Hochberg considered in addition a closed chemical system (*i.e.* the total mass of matter is kept constant) which allows polymers to grow towards a finite length (see reaction scheme in Fig. 24).[64] Starting from an infinitesimal e.e. bias (e.e.$^0$ = 5 × 10$^{-8}$%), the model shows the emergence of homochiral polymers in an absolute but temporary manner. The reversibility of this SMSB process was expected for a closed system. Ma and co-workers recently published a probabilistic approach which is presumed to better reproduce the emergence of the primeval RNA replicators and ribozymes in the RNA World.[576] The D-nucleotide and L-nucleotide precursors are set to racemize to account for the behaviour of glyceraldehyde under prebiotic conditions; and the polynucleotide synthesis is surface- or template-mediated. The emergence of RNA polymers with RNA replicase or nucleotide synthase properties during the course of the simulation led to amplification of the initial chiral bias. Finally, several models show that cross-inhibition is not a necessary condition for the emergence of homochirality in polymerization processes. Higgs and co-workers considered all polymerization steps to be random (*i.e.* occurring with the same rate constant) regardless of the nature of condensed monomers and that a fraction of homochiral polymers catalyzes the formation of the monomer enantiomers in an enantiospecific manner.[577] The simulation yielded homochiral polymers (of both antipodes) even from a pure racemate under conditions which favour the catalyzed over non-catalyzed synthesis of the monomers. These polymers are referred to as "chiral living polymers" as the result of their auto-catalytic properties. Hochberg modified its previous kinetic reaction scheme drastically by suppressing cross-inhibition (polymerization operates through a stereoselective and cooperative mechanism only), and by allowing fragmentation and fusion of the homochiral polymer chains.[578] The process of fragmentation is irreversible for the longest chains, mimicking a mechanical breakage. This breakage represents an external energy input to the system. This binary chain fusion mechanism is necessary to achieve SMSB in this simulation from infinitesimal chiral bias (e.e.$^0$ = 5 × 10$^{-11}$%). Finally, even though not specifically designed for a polymerization process, a recent model by Ribó and Hochberg shows how homochiral replicators could emerge from two or more catalytically coupled asymmetric replicators, again without the need for the inclusion of a heterochiral inhibition reaction.[350] Six homochiral replicators emerge from their simulation by means of an open flow reactor incorporating six achiral precursors and replicators in low initial concentrations and minute chiral biases ($\text{e.e.}^0 = 5 \times 10^{-18}\%$). These models should stimulate the quest of polymerization pathways which include stereoselective ligation, enantioselective synthesis of the monomers, replication and cross-replication, *i.e.* hallmarks of an ideal stereoselective polymerization process.

### 5.4 Purely biotic scenarios

In the previous two sections, the emergence of BH was dated at the level of prebiotic building blocks of life (for purely abiotic theories) or at the stage of the primeval replicators, *i.e.* at the early or advanced stages of the chemical evolution, respectively. In most theories, an initial chiral bias was amplified yielding either prebiotic molecules or replicators as single enantiomers. Others hypothesized that homochiral replicators and then life emerged from unbiased racemic mixtures by chance, basing their rationale on probabilistic grounds.[17,421,559,577] In 1957, Fox,[579] Rush[580] and Wald[581] held a different view and independently emitted the hypothesis that BH is an inevitable consequence of the evolution of the living matter.[44] Wald notably reasoned that, since polymers made of homochiral monomers likely propagate faster, are longer and have stronger secondary structures (*e.g.* helices), they must have provided sufficient criteria to the chiral selection of amino acids thanks to the formation of their polymers under *ad hoc* conditions. This statement was supported by experiments showing that stereoselective polymerization is enhanced when oligomers adopt a α-helix conformation.[485,528] However, Wald went a step further by supposing that homochiral polymers of both handedness would have been generated under the supposedly symmetric external forces present on prebiotic earth and that primordial life originated under the form of two populations of organisms, enantiomers of each other. From then, the natural forces of evolution led certain organisms to be superior to their enantiomorphic neighbours leading to life in a single form, as we know it today. The purely biotic theory of emergence of BH thanks to biological evolution, instead of chemical evolution for abiotic theories, was accompanied by large scepticism in the literature even though the arguments of Wald were developed later on by others[44] and notably by Ageno (sexual reproduction naturally resolves enantiomeric populations),[582] and Kuhn (the stronger enantiomeric form of life survived in the ''struggle'').[583] More recently, Green and Jain summarized the Wald theory into the catchy formula ''Two Runners, One Tripped'',[584] and called for deeper investigation on routes towards racemic mixtures of biologically relevant polymers.

The Wald theory by its essence has been difficult to assess experimentally. On the one side, (*R*)-amino acids when found in mammals are often related to destructive and toxic effects suggesting a lack of complementary with the current biological machinery in which (*S*)-amino acids are ultra-predominating. On the other side, (*R*)-amino acids have been detected in the cell wall peptidoglycan layer of bacteria[585] and in various peptides of bacteria, archaea, and eukaryotes.[16] (*R*)-Amino acids in these various living systems have an unknown origin. Certain proponents of the purely biotic theories suggest that the small but general occurrence of (*R*)-amino acids in nowadays living organisms can be a relic of a time in which mirror-image living systems were ''struggling''. Likewise, to rationalize the aforementioned ''lipid divide'', it has been proposed that the LUCA of bacteria and archaea could have embedded a heterochiral lipid membrane, *i.e.* a membrane containing two sorts of lipid with opposite configurations.[521]

Several studies also probed the possibility to prepare a biological system containing the enantiomers of the molecules

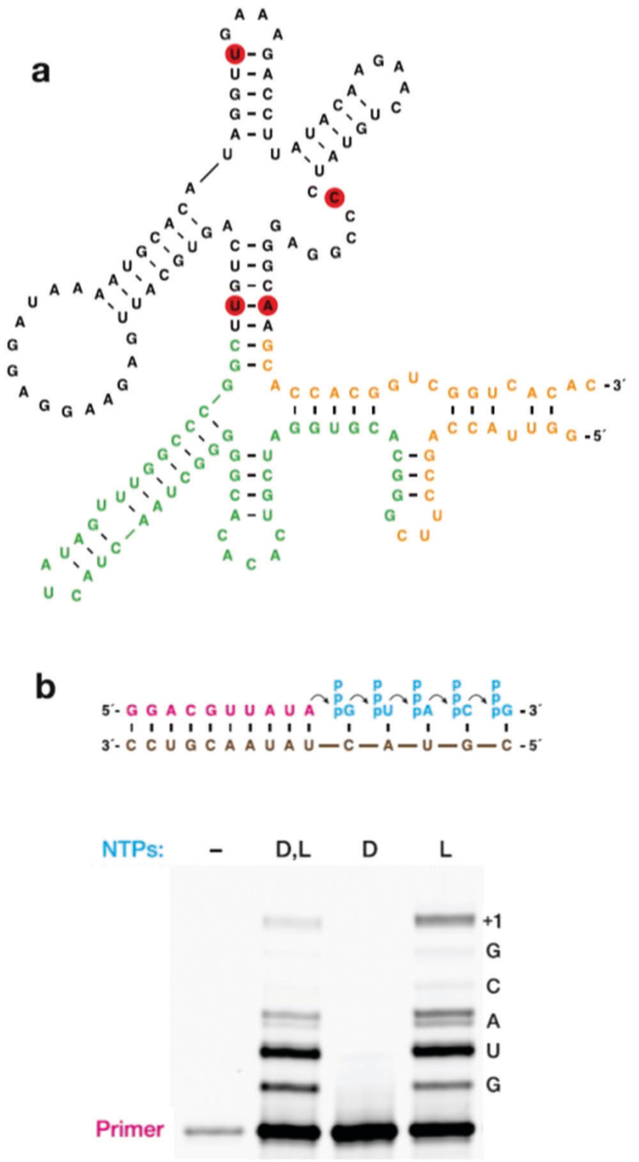

Fig. 25 Cross-chiral ribozyme. (a) Sequence and secondary structure of the 42.9t ribozyme. Structural evolutions from the starting 16.12t ribozyme are indicated as follow: core of the 16.12t ribozyme (black), optimized nucleotide sequence (green) and primer binding sites (orange). Red circles indicate mutations relative to the core of the starting 16.12t ribozyme. (b) RNA-templated polymerization, demonstrating incorporation of all four L-NTPs, but not D-NTPs. The experiments are conducted with a L-RNA primer connected to the D-ribozyme, in presence of a separate L-RNA template, in order to direct the synthesis of a product having the sequence 5′-GUACG-3′. Reproduced with permission from ref. 590. Copyright 2020. American Chemical Society.

of life as we know it today. L-Polynucleotides and (*R*)-polypeptides were synthesized; and expectedly they exhibited chiral substrate specificity and biochemical properties that mirrored those of their natural counterparts.[586–588] In a recent example, Liu, Zhu and co-workers showed that a synthesized 174-residue (*R*)-polypeptide catalyzes the template-directed polymerization of L-DNA and its transcription into L-RNA.[587] It was also demonstrated that the synthesized and natural DNA polymerase systems operate without any cross-inhibition when mixed together in the presence of a racemic mixture of the constituents required for the reaction (D- and L primers, D- and L-templates and D- and L-dNTPs). From these impressive results, it is easy to imagine how mirror-image ribozymes would have worked independently in the early evolution times of primeval living systems.

One puzzling question concerns the feasibility for a biopolymer to synthesize its mirror-image. This has been addressed elegantly by the group of Joyce who demonstrated very recently the possibility for a RNA polymerase ribozyme to catalyze the templated synthesis of RNA oligomers of the opposite configuration.[589] The D-RNA ribozyme was selected, through 16 rounds of selective amplification away from a random sequence, for its ability to catalyze the ligation of two L-RNA substrates on a L-RNA template. The 16.12t D-RNA ribozyme was eventually discovered which exhibited sufficient activity to generate full-length copies of its enantiomer through the template-assisted ligation of 11 oligonucleotides. Variants of this cross-chiral enzyme demonstrated stronger ability to polymerize nucleotide triphosphates (NTP) and trinucleotides.[590] Importantly, these designed ribozymes (such as the NTP polymerase shown in Fig. 25) remain operative in the presence of racemic substrates and templates. In the hypothesis of a RNA world, it is intriguing to consider the possibility of a primordial ribozyme with cross-catalytic polymerization activities. In such a case, one can consider the possibility that enantiomeric ribozymes would have existed concomitantly and that evolutionary innovation would have favoured the systems based on D-RNA and (*S*)-polypeptides leading to the exclusive form of BH as present on earth nowadays. Finally, a strongly convincing evidence for the standpoint of the purely biotic theories would be the discovery in sediments of primitive forms of life based on a molecular machinery entirely composed of (*R*)-amino acids and L-nucleic acids.

## 6. Conclusions and perspectives of biological homochirality studies

Questions accumulated while considering all the possible origins of the initial enantiomeric imbalance that have ultimately led to biological homochirality. When some hypothesize a reason behind its emergence (such as for informational entropic reasons, resulting in evolutionary advantages towards more specific and complex functionalities),[25,350] others wonder whether it is reasonable to reconstruct a chronology 3.5 billion years later.[37] Many are circumspect in front of the pile-up of scenarios and assert that the solution is likely not expected in a near future (due to the difficulty to do all required control experiments, and fully understand the theoretical background of the putative selection mechanism).[53] In parallel, the existence, and the extent, of a putative link between the different configurations of biologically relevant amino acids and sugars also remains unsolved,[591] and only Goldanskii and Kuz'min studied the effects of a hypothetical global loss of optical purity in the future.[429]

Nevertheless, great progress has been made recently for a better perception of this long-standing enigma. The scenario involving circularly polarized light as a chiral bias inducer is more and more convincing thanks to operational and analytical improvements. Increasingly accurate computational studies supply precious information, notably about SMSB processes, chiral surfaces, and other truly chiral influences. Asymmetric autocatalytic systems and deracemization processes have also undoubtedly grown in interest (notably thanks to the discoveries of the Soai reaction and the Viedma ripening). Space missions are also an opportunity: to study the *in situ* organic matter, its conditions of transformations, and possible associated enantio-enrichment; to elucidate the solar system origin and its history; and maybe, to find traces of chemicals with "unnatural" configurations in celestial bodies, which could indicate that the chiral selection of terrestrial BH could be a mere coincidence.

The current state of the art indicates that further experimental investigations of the possible effect of other sources of asymmetry are needed. Photochirogenesis is attractive in many respects: CPL has been detected in space, e.e. values have been measured for several prebiotic molecules found on meteorites or generated in laboratory-reproduced interstellar ices. However, this detailed postulated scenario still faces pitfalls related to the variable sources of extra-terrestrial CPL, the requirement of finely-tuned illumination conditions (almost full extent of reaction at the right place and moment of the evolutionary stages), and the unknown mechanism leading to the amplification of the original chiral biases. Strong calls to organic chemists are thus necessary to discover new asymmetric autocatalytic reactions, maybe through the investigation of complex and large chemical systems,[592] that can meet the criteria of primordial conditions.[40,41,302,312]

Anyway, the quest for the biological homochirality origin is fruitful in many aspects. The first concerns one consequence of the asymmetry of life: the contemporary challenge of synthesizing enantiopure bioactive molecules. Indeed, many synthetic efforts are directed towards the generation of optically-pure molecules, to avoid potential side effects of racemic mixtures due to the enantioselectivity of biological receptors. These endeavors can undoubtedly draw inspiration from a range of deracemization and chirality induction processes conducted in connection with biological homochirality. One example is the Viedma ripening, which allows the preparation of enantiopure molecules displaying potent therapeutic activities.[55,593] Other efforts are devoted to the building-up of sophisticated experiments and pushing their measurement limits to be able to detect tiny enantiomeric excesses, thus strongly contributing to important improvements in scientific instrumentation and acquiring fundamental knowledge at the interface between chemistry, physics, and biology. Overall, this joint endeavor at the frontier of many fields is also beneficial to materials science notably for the elaboration of biomimetic materials and emerging chiral materials.[594,595]

## Abbreviations

| | |
|---|---|
| BH | Biological homochirality |
| CISS | Chiral-induced spin selectivity |
| CD | Circular dichroism |
| de | Diastereomeric excess |
| DFT | Density functional theories |
| DNA | Deoxyribonucleic acid |
| dNTPs | Deoxynucleotide triphosphates |
| e.e(s). | Enantiomeric excess(es) |
| EPR | Electron paramagnetic resonance |
| Epi | Epichlorohydrin |
| FCC | Face-centred cubic |
| GC | Gas chromatography |
| LES | Limited enantioselective |
| LUCA | Last universal cellular ancestor |
| MCD | Magnetic circular dichroism |
| MChD | Magneto-chiral dichroism |
| MS | Mass spectrometry |
| MW | Microwave |
| NESS | Non-equilibrium stationary states |
| NCA | *N*-Carboxy-anhydride |
| NTPs | Nucleotide triphosphates |
| NMR | Nuclear magnetic resonance |
| OEEF | Oriented-external electric fields |
| Pr | Pyranosyl-ribo |
| PV | Parity violation |
| PVED | Parity-violating energy difference |
| REF | Rotating electric fields |
| RNA | Ribonucleic acid |
| SDE | Self-disproportionation of the enantiomers |
| SEs | Secondary electrons |
| SMSB | Spontaneous mirror symmetry breaking |
| SNAAP | Supernova neutrino amino acid processing |
| SPEs | Spin-polarized electrons |
| VUV | Vacuum ultraviolet |

## Author contributions

QS selected the scope of the review, made the first critical analysis of the literature and wrote the first draft of the review. JC modified Parts 1, 2 and 3.1 according to her expertise in the domains of chiral physical fields and parity violation. MR re-organized the review into its current form and extended Parts 3–5. All authors were involved in the revision and proof-checking of the successive versions of the review.

## Conflicts of interest

There are no conflicts to declare.

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