ABSOLUTE ASYMMETRIC SYNTHESIS: A COMMENTARY

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Dedicated to the memory of Professor Otakar Červinka.

Absolute asymmetric synthesis, *i.e.*, the formation of enantiomerically enriched products from achiral precursors without the intervention of chiral chemical reagents or catalysts, is in practice unavoidable on statistical grounds alone. That random chance, combined with suitable amplification mechanisms, might ultimately account for biomolecular homochirality in Nature was recognized more than a century ago. Soai and collaborators have recently developed an asymmetric autocatalysis reaction that is capable of amplifying a tiny enantiomeric excess of far below 1% to yield a nearly enantiopure product. Although there is no easy way to tell the difference between an asymmetric autocatalysis reaction initiated by the tiny enantiomeric excess due to random chance and one initiated by minuscule quantities of unidentified chiral impurities, it is nevertheless all but certain that the Soai reaction is capable of producing optically active compounds by an absolute asymmetric synthesis, starting from nominally achiral reagents free of chiral contaminants and run under achiral conditions, *e.g.*, without the intervention of chiral physical forces.

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As is well known, each of life's crucial biomolecules – amino acids, sugars, biopolymers – "has its own unique and constant sense of chirality, which is characterized further by essentially complete enantiomeric homogeneity"[1a]. How this biomolecular homochirality originated in Nature is shrouded in mystery. Yet, although the actual origin of terrestial homochirality, and the origin of life on Earth, cannot be established with absolute certainty and will thus forever remain a closed book, there has been no shortage of ingenious speculations, many of them inspiring theories and experiments that ultimately enriched our understanding of chemistry[1].

Absolute Asymmetric Synthesis Defined

Among such speculations, there is one that postulates "formation of enantiomerically enriched products from achiral precursors without the intervention of pre-existing optical activity, namely absolute asymmetric synthesis and the amplification of chirality"[2]. Accordingly, we adopt the following definition:

– *Absolute asymmetric synthesis* is the formation of enantiomerically enriched products from achiral precursors without the intervention of chiral chemical reagents or catalysts.

This represents a significant departure from the original definition by Bredig[3], who first introduced this term in 1923, in which "asymmetric external physical forces" played a crucial role:

– "Die hier mitzuteilenden Versuche sollten als Vorstudie dienen zu dem Ziele, *optisch dauernd aktive Stoffe*, nicht wie bisher unter Anwendung *schon vorhandener* optisch aktiver Stoffe (entweder durch direkten äquivalenten Umsatz oder durch katalytische Wirkung derselben) zu erzeugen, sondern sogar ohne jede Mitwirkung vorher schon vorhandener optisch aktiver Stoffe *lediglich durch Einwirkung asymmetrischer äusserer physikalischer Kräfte* entstehen zu lassen. Eine solche '*absolute*' asymmetrische Synthese (oder Spaltung) z. B. durch magnetische, elektrische oder photochemische Kräfte ist schon wiederholt, aber bisher stets vergeblich versucht worden."

Bredig's definition, with its emphasis on the need for the intervention of asymmetric physical forces, has been echoed in authoritative texts, as shown by the following examples:

– P. D. Ritchie (1947)[4]: "*Absolute asymmetric synthesis*. Optically selective formation of dissymmetric [*i.e.*, chiral] molecules by the interaction of symmetrical molecules or groups under the influence of an unsymmetrical physical agency (*e.g.*, circularly polarized light)."

– E. L. Eliel (1962)[5]: "[Absolute asymmetric syntheses] are syntheses of compounds in active form without the intervention of any dissymmetric chemicals. Some sort of physically dissymmetric influence is required in such syntheses, and it is necessary that the physical agent in question be essential to the synthesis, rather than accidental to it."

– J. D. Morrison and H. S. Mosher (1971)[6]: "Absolute asymmetric synthesis includes only those processes which result in the formation of a chiral product without the intervention of any other chiral *chemical* reagent, and thus it is limited to those chiral processes brought about by a chiral physical force, *i.e.*, elliptically or circularly polarized light. By broadly interpreting the term 'chiral reagent' to include chiral physical force, the original

definition of asymmetric synthesis encompasses those processes known by the term *absolute asymmetric synthesis*. It is required that the chiral physical force be necessary for the reaction in question, *i.e.*, that without the physical force the reaction will not proceed. Without this condition there is no rational basis for the reaction to take a chiral course."

– W. Bähr and H. Theobald (1973)[7]: "Als 'absolute' (gelegentlich auch 'totale') asymmetrische Synthese bezeichnet man die Herstellung optisch aktiver Substanzen aus inaktivem Ausgangsmaterial unter chiralen physikalischen Einflüssen, also ohne jedes optisch aktive Hilfsreagenz."

– V. I. Sokolov (1991)[8]: "Asymmetric synthesis in the absence of asymmetric chemical reagents, including those acting as catalysts, is usually called *absolute* asymmetric synthesis. In order to ensure that when a chiral molecule appears the enantiomeric configurations were formed in unequal quantities, the action of a physically asymmetric agent is necessary."

– R. E. Gawley and J. Aubé (1996)[9]: "*Absolute asymmetric synthesis*: A synthesis in which achiral reactants are converted to nonracemic, chiral products, and where the enantioselectivity is induced only by an external force such as circularly polarized light in a photochemical reaction."

The Bredig-derived definitions are, however, unnecessarily restrictive. First, there is no need for an external chiral physical influence, such as circularly polarized light, because the small but persistent PVEDs (parity-violating energy differences) between enantiomers due to the intrinsic chirality inherent in all matter might suffice to explain the mystery of biomolecular homochirality[1,10]. More importantly, it has been recognized that determinate mechanisms[1a], *i.e.*, the intervention of chiral physical forces or fields, whether external or intrinsic, are not the only means of achieving some degree of enantiomeric excess in absolute asymmetric syntheses. The reason is that enantiomerically enriched products are bound to be formed from achiral precursors merely as a result of statistical fluctuations, *i.e.*, by purely stochastic processes[1,11].

On the Inevitability of Enantiomeric Enrichment in Absolute Asymmetric Syntheses

To see why this must be so, consider a familiar analogy: the statistics of tossing fair coins. While there is an even chance of obtaining heads or tails in a single flip, the probability that exactly 50 heads and 50 tails will turn up in 100 throws is only 0.080. It is close to impossible to obtain exactly 500,000 heads and an equal number of tails in a set of one million tosses. Instead, with a high degree of probability approaching virtual certainty,

hundreds of heads will be in excess over tails, or *vice versa*. This analogy is readily translated into the realm of chemistry. For example, consider reduction of butan-2-one with $LiAlH_4$ under achiral conditions. The two faces of a coin are now represented by the enantiotopic faces of the carbonyl group, and the tossing to yield heads or tails by $LiAlH_4$ attack to yield (*R*)- or (*S*)-butan-2-ol. Reduction of butan-2-one under achiral conditions is thus all but certain to yield a racemic mixture of butan-2-ol slightly enriched, by this stochastic process, in one of the two enantiomers. In short, *absolute asymmetric synthesis, even in the absence of chiral physical forces, is in practice unavoidable on statistical grounds alone*. Note that the probability of any given experiment yielding a certain excess of one rather than the other enantiomer (*e.g.*, *S* rather than *R*) is exactly one half, so that overall parity is still conserved for a statistically significant number of experiments.

That random fluctuations, combined with suitable amplification mechanisms, might ultimately account for biomolecular homochirality in Nature was clearly recognized more than a century ago by Pearson[12]. In his forceful rebuttal of a statement by Japp[13a], who, in a major address earlier that year on "Stereochemistry and Vitalism", had asserted that "the chance synthesis of the simplest optically active compound from inorganic materials is absolutely inconceivable", Pearson retorted[12b]: "To this I replied and still reply, it is *not* absolutely inconceivable. An optically active compound means merely a preponderance of one kind of enantiomorph, and *chance* will always produce this, given enough trials and length of time to make them... The statement that on the theory of *chance*, an optically active compound is *absolutely inconceivable* is, I take it, absurd. It may be very *improbable*, but this is not the term used by Prof. Japp".

In 1929, Gilman[14a], though unaware of Pearson's arguments ("We make no claim for the novelty of the ideas expressed here, but we are not familiar with like material published elsewhere") significantly enlarged on this theme by showing – as he had in his classroom teachings for a number of years[14b] – that by "application of the statistical theory of probability...direct [*i.e.*, absolute] asymmetric syntheses may frequently take place".

Consider a macroscopic racemic sample such as, to take our example, the product of reduction of butan-2-one under achiral conditions. Because the probability is exactly one half that this sample consists of an odd number of molecules, there is an even chance that *at least* one chiral molecule, either (*R*)- or (*S*)-butan-2-ol, remains uncompensated. Thus, according to Gilman, no sample comprised of an odd number of molecules can be *strictly* racemic. But even if the sample has an even number of molecules, the probability is vanishingly small that it is strictly racemic, in the sense of being

composed of enantiomers an *exactly* equimolar proportions. Gilman concluded that "It is apparent from these considerations that the chemist actually does effect unwittingly direct asymmetric syntheses." Or, as Mills[15] later put it: "It is practically impossible for the product to be absolutely optically inactive". The evolution of homochirality in Nature from abiotic sources can thus be simply accounted for on the basis of such statistical arguments[16].

Pearson[12a] had earlier predicted that "if a chemist were to spend his life in the preparation of innumerable and smallest physically sensible amounts of a normally racemoid substance, he would with fine enough apparatus ultimately be able to detect some amount of rotatory polarisation." Gilman[14a] went a step further: "The possibility of getting a complete conversion of *n* molecules (where *n* is either even or odd) to the *dextro* or to the *levo* form obviously decreases with an increase in the number of molecules... [Nevertheless] we would, sometime or other if a sufficient number of experiments were performed, get a complete conversion to the *dextro* or to the *levo* form in accordance with the statistical theory of probability. The number of experiments necessary to reach this fortuitous complete conversion to an optically active form would be extreme, but not infinite." In a footnote, he added that "It would not be surprising if a few (an astonishingly small number) of the abnormal, non-duplicable results observed by some investigators were not due to such a happy or unhappy 'accident' postulated by the statistical theory of probability...[but] there would be a pardonable and understandable reluctance to publish a finding of this type".

No such reluctance inhibited the authors of a paper that appeared in 1944, and in which they reported obtaining optically active santonin, a naturally occurring product, by synthesis from achiral precursors under achiral conditions[17]. Their implausible claim, embellished with the allegation that "So far as we are aware, this is the first total [*i.e.*, absolute] asymmetric synthesis, apart from asymmetric synthesis carried out in the presence of polarized light, *etc.*", was of course immediately challenged[18]. While their results were, unsurprisingly, found to be irreproducible, Cornforth *et al.*[18a] put the matter in its proper perspective by observing that "Such an asymmetric synthesis from inactive materials violates no fundamental law and might theoretically be expected to occur once in about $(10^{10})^{20}$ trials." Much as "in that unreal world where a fount of type, if jumbled together sufficiently often, ends by setting up the text of *Hamlet*"[13b].

It was Mills[15] who first reported a quantitative treatment (by L. A. Pars) of the statistical fluctuations that might at a guess be responsible for the origin of biomolecular homochirality. The enantiomeric excess ("degree of sta-

tistical dissymmetry"[15]) k is related to N, the total number of molecules in the sample, by

$$k = 0.6743/\sqrt{N} .$$

The magnitude of the statistical fluctuation depends on the size of the sample: with increasing size of sample, the number of enantiomeric molecules in excess, kN, increases while k, and with it the probability of obtaining a strictly racemic sample, decreases. Thus, if the reduction of butan-2-one is carried out under achiral conditions on a large number of samples each containing a million molecules, $k = 6.7 \times 10^{-4}$, *i.e.*, half the samples will contain an excess of more than 674 molecules of either (*R*)- or (*S*)-butan-2-ol. More realistically, if we start with a roughly millimolar (*i.e.*, laboratory-size) sample of, say, 10^{20} molecules, there is an even chance of obtaining a product containing an excess of 6.7×10^9 molecules, a huge increase of kN that is matched by an equally pronounced decrease of k to 6.7×10^{-11}.

Even the most powerful measuring device available today is incapable of detecting a significant difference between a racemic sample with such a minuscule enantiomeric excess and one that is composed of an *exactly* equimolar mixture of enantiomers. We have called the former "cryptochiral", because the model of the sample demands an excess of one enantiomer over the other in the time domain of observation, and so is chiral, but the chirality phenomenon falls below the threshold of observation and is thus literally hidden from observation[19]. In other words, when a molecular aggregate containing an excess of one enantiomer is examined and characterized by its physical and/or chemical properties, and if these do not include observable chiroptical or other chirality properties even though the geometry of the individual molecules is chiral, then the aggregate is justifiably and logically designated as being cryptochiral. We stress this point because failure to grasp this elementary distinction between the model of the molecular ensemble and the model of the individual molecule has led to a profound misunderstanding of what is meant by cryptochirality[20a], and has in turn inspired misdirected circumlocutions, *e.g.*, "crypto optical activity"[20b].

The preceeding discussion induces a question: can a sample whose enantiomeric excess lies that far below the observational horizon still be properly regarded as chiral? We briefly digress to examine this semantic problem in further detail[19].

Chirality as a Primitive Fuzzy Concept

On the basis of any conceivable experimental observation, a sample of butan-2-ol with an enantiomeric excess (ee = $|(R - S)/(R + S)|$) of, say, $(10^{20} - 1)/(10^{20} + 1)$, *i.e.*, a sample containing just one molecule of (*S*)-butan-2-ol to 10^{20} molecules of the *R* isomer, is operationally indistinguishable from one that is enantiomerically pure in the strictest sense (ee = 1). On the other hand, a roughly millimolar sample containing just one molecule of (*S*)-butan-2-ol in excess over the *R* isomer (ee = $1/(10^{20} + 1)$) would appear to be achiral because any chirality property measured on it would fall way below the observational threshold. Yet it might be rightly argued that a sample with even such a minute ee value cannot properly be considered achiral, since, if it were to be so regarded, one would then be forced into the position of having to admit to the existence of an ee value, somewhere between $1/(10^{20} + 1)$ ("achiral") and 1 (chiral and enantiopure), beyond which the mixture could no longer be described as achiral. This value would vary, depending on the particular chirality property, and would furthermore be tied to the observational threshold (which in turn depends on measurement sensitivity, conditions of measurement, *etc.*). By way of this argument – which is analogous to the classical question of whether a man with only one more hair than a bald man is still bald – one is inexorably led to the conclusion that it is impractical as well as unreasonable to draw a sharp line between chiral and achiral molecular ensembles. Thus, in contrast to the crisp classification of geometrical objects into chiral and achiral ones, in the present case one deals with a fuzzy borderline distinction, and the qualifying "operationally" must be implicitly attached to "achiral" or "racemic" whenever one uses these terms with reference to observable properties of a macroscopic sample.

In short, the principle of cutting, *i.e.*, a partitioning into the equivalence classes "chiral" and "not-chiral", is inapplicable in fuzzy categories. This can create curious paradoxes. For example, the term "nonracemic", which may refer either to an enantiomerically enriched or to an enantiopure substance[21], is fuzzily linked to its antonym "racemic" because, as we saw, a bulk sample comprised of *exactly* equimolar quantities of enantiomers belongs to the fictitious realm of an idealized model. It is natural to abandon two-valued logic in the actual practice of science because, when one deals with the phenomena of nature, one enters "a stage in logic in which we recognize the utility of imprecision"[22]. The vagueness of "chiral" and "achiral", when these terms are employed with reference to a chemical system, should therefore be regarded as a useful virtue rather than as a defect,

just like other paired terms familiar to chemists that are fuzzily defined yet undeniably useful, such as fast/slow, strong/weak, concentrated/dilute, hot/cold.

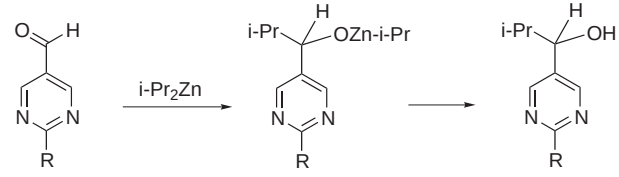
Amplification of a Minuscule Enantiomeric Bias by Asymmetric Autocatalysis

We saw that the production of enantiomeric excesses by random chance is for all intents and purposes unavoidable. But what is needed to produce "a sensible quantity of substance"[13b] that is recognizably chiral as judged, *e.g.*, on the basis of its optical activity, is an amplification process that significantly increases the tiny excess produced by random fluctuations. Such a process would complete the counterargument to Japp's "contention that single asymmetric forms cannot arise under chance conditions"[13b], and to his view that "No fortuitous concourse of atoms, even with all eternity for them to clash and combine in, could compass this feat of the formation of the first optically active organic compound"[13a].

There are, in general, numerous processes – so-called "asymmetric amplifications" or "amplifications of chirality" – that lead to an increase in enantiopurity[1a,23], and there were early considerations of ways in which random fluctuations in racemic mixtures might thus be enhanced[24]. A breakthrough occurred when it was recognized by Frank[25], and, independently but later, by others[26], that autocatalytic processes in which "a chemical substance which is a catalyst for its own production and an anti-catalyst for the productions of its optical antimer"[25] are in theory capable of transforming extremely small enantiomeric excesses into "a sensible quantity of substance". In Mason's words[27], Frank's kinetic processes "are Darwinian in form".

Recent years witnessed a variety of studies on the topic of asymmetric autocatalysis[28–31], but it was not until 1995 that Frank's theoretical scheme of 1953 was brought to life in a spectacular experimental demonstration by Soai *et al.*[32] of asymmetric autocatalysis with amplification of enantiopurity. As shown in Scheme 1, reaction of diisopropylzinc with pyrimidine-5-carbaldehyde (**1a**, R = H) in toluene yields an adduct, diisopropylzinc alkoxide **2a**, which on hydrolysis produces 2-methyl-1-(pyrimidin-5-yl)-propan-1-ol (**3a**). In this ground-breaking work, Soai *et al.* showed that when **1a** was allowed to react with diisopropylzinc in the presence of the "chiral initiator" (*S*)-**3a** (2% ee), hydrolysis of **2a** yielded (*S*)-**3a** with an enhanced ee of 10%. Use of this carbinol as the catalyst in a subsequent round produced (*S*)-**3a** with an ee of 57%, and two additional cycles yielded (*S*)-**3a**

with ee's of 81 and 88%, respectively. It was a striking demonstration of asymmetric amplification by "automultiplication". In extensions of this reaction[33,34], Soai and coworkers succeeded in providing additional and equally impressive examples of asymmetric autocatalysis with amplification of enantiopurity, whether by use of heterocycles other than **1** (*e.g.*, quinoline-3-carbaldehyde) or by the introduction of ring substituents (Scheme 1, R ≠ H); furthermore, the chiral initiators were greatly varied and included, *inter alia*, chiral crystals (quartz, sodium chlorate), α-amino acids, octahedral cobalt complexes, and α-deuterated benzyl alcohol.



1 **2** **3**

SCHEME 1

The sensitivity and efficiency of asymmetric amplification in the Soai reaction is truly astounding: trace amounts of chiral additives (*i.e.*, chiral initiators) with extremely low ee's can be made to yield nearly enantiopure product. For example, (*S*)-1-[2-(*tert*-butylethynyl)pyrimidin-5-yl]-2-methylpropan-1-ol **3b** [33g] (Scheme 1, R = *tert*-butylethynyl) with an ee of 0.6% was automultiplied during four consecutive **1b** → **3b** reactions to yield (*S*)-**3b** with >99.5% ee [34c,35]. More recently, Soai and coworkers reported that after three consecutive reactions, (*R*)- and (*S*)-**3b** with an ee of only *ca* 0.00005% yielded (*R*)- and (*S*)-**3b**, respectively, with >99.5% ee [33r]. In their contemporaneous and independent study of the reaction sequence **1c** → **3c** (Scheme 1, R = CH_3), Singleton and Vo found that initiation by (*R*)-2-methyl-1-(2-methylpyrimidin-5-yl)propan-1-ol (**3c**) with an ee of only 0.00003% afforded (*R*)-**3c** with 71% ee after four consecutive reactions[36].

Soai and coworkers also investigated the kinetics of their reaction[33l]. According to an independent and contemporaneous kinetic study by Blackmond *et al.*[37a], "a simple dimeric catalyst model", envisaged as a bimetallic chelate comprised of two homo- or heterochiral molecules of **2c**, "explains the broad features of [Soai's] asymmetric autocatalysis". Suppression of the production of the minor enantiomer, a crucial feature of their kinetic model, is conceptually related to Frank's anti-catalysis. Such inhibition is "indispensable to asymmetric amplification in autocatalysis" since otherwise "product (catalyst) ee will inexorably decrease over time"[37b].

Can the Soai Reaction Function as an Absolute Asymmetric Synthesis?

The extraordinary power of the Soai asymmetric amplification reaction to transform the ee's of carbinols from far below 1% to nearly 100% immediately raises a fascinating question that brings us back to a central theme of this essay: might the enantiomeric excess due to random fluctuations in a racemic homogeneous system, though almost vanishingly small (in the order of, say, 10^{-9}%), be nevertheless sufficient to yield an enantiopure product by this (or a similar) process of automultiplication? Such an absolute asymmetric synthesis, involving as it does the formation of an optically active product from achiral reagents under the exclusion of added chiral initiators and of chiral physical forces (*e.g.*, circularly polarized light), might seem to fly in the face of Japp's dictum[13a] that "Only asymmetry can beget asymmetry". But this dictum remains inviolate in the present case because the optically active product is obtained by autocatalytic amplification of a racemic mixture that is *cryptochiral*, thanks to the tiny enantiomeric excess resulting from symmetry breaking by a stochastic process.

In their first attempt to address this question, Soai *et al.* explored the formation of enantiomerically enriched alkanols of type **3** by their method, but *without* making use of any physical or chemical chiral initiators. The optically active alkanols thus produced sometimes had the *S* and sometimes the *R* configuration. Their observations, described in a 1997 patent[38], were of sufficient interest to merit citation in a review on chiral autocatalysis, spontaneous symmetry breaking, and stochastic behavior[39]. The patent did not disclose the actual enantiomeric distribution ratio, nor did it offer any theoretical speculation on that ratio which, as was subsequently revealed[33r], deviated significantly from unity.

With the same goal in mind, Singleton and Vo recently studied the automultiplication reaction **1c** → **3c** without the intervention of any physical or chemical chiral initiators[36]. They found that each of 48 trials "ultimately afforded substantial optical activity in the product" after two to eight cycles, with widely varying ee's and an *R* to *S* ratio of 10 to 38. Yet despite a "considerable effort to purify reagents and avoid experimental contamination with dust", the authors concluded that "there is substantial evidence" that "the ultimate optical activity [of **3c**] arises from optically active impurities" and that therefore "most (and likely all) of these reactions are not true examples of absolute asymmetric synthesis". The solvents (toluene, benzene, diethyl ether), though scrupulously purified, were believed to be the major source of the optically active contaminants.

Despite many careful control experiments, Singleton and Vo failed in their efforts to detect, let alone identify, the suspected contaminants. The evidence that chiral impurities in trace amounts are responsible for the observed optical activity of **3c**, while plausible, thus falls short of being compelling. That is, the authors' conclusions are properly characterized by the Scottish verdict of "not proven". Before we explore the implications of this verdict, however, let us assume for the moment that the authors are right and that optically active impurities in common organic solvents did indeed function as the chiral initiators in "most (and likely all) of these reactions". The molecules of toluene, benzene, and diethyl ether are of course achiral, yet the chiral contaminants render macroscopic samples of these solvents "barely (or feebly) chiral", in the language of fuzzy logic. The situation parallels the one discussed for racemic samples, with the difference that the impurities in samples of achiral solvents differ from the "host" molecules in chirality and in constitution, whereas the slight enantiomeric excess in racemic samples is constitutionally the same as the rest of the molecules. We are thus faced again with an extreme example of cryptochirality: the model – in this case a mixture of chiral and achiral molecules in a macroscopic sample – is chiral, but, because there is no more than a trace of chiral component in the mixture, no chirality properties are detectable. With respect to such properties, the solvent thus behaves as expected, *i.e.*, as though it were wholly achiral. If Singleton and Vo got it right, we may therefore have to get used to the idea that chiral trace impurities are ubiquitous and all-pervasive, and that many, if not most, so-called achiral materials – solvents, reagents, catalysts – are in fact cryptochiral. The work of Singleton and Vo further underscores the fact that "purity" in real-world systems has meaning only in the fuzzy sense[19a]; even if we could purge nominally pure achiral solvents of their trace chiral impurities, assuming that we knew what they were, how to detect them, and how to get rid of them, how could we convincingly show that they had been *completely* removed given that this would require proof of an unverifiable negative?

But let us now assume – *pace* Singleton and Vo – that of the 48 trials resulting in measurable optical activity, at least a few, and possibly many, had *not* been triggered by chiral impurities. There is no way that such a possibility can be excluded on the basis of the evidence presented by the authors. Admittedly, the probability of obtaining a 10:38 ratio of enantiomers, 2.32×10^{-5}, happens to be almost exactly the same as the probability of obtaining 30 heads and 70 tails in 100 throws of a coin, a result that strongly suggests that the coin is biased to give preference to one of the two faces: a metaphor for the effect of hidden chiral impurities. Nevertheless,

the possibility cannot be dismissed that an unknown number of trials resulted in truly absolute asymmetric syntheses, *i.e.*, syntheses that were *not* initiated by impurities. But it is impossible to say how many – or, for that matter, whether there were any at all. In that sense, the results reported by Singleton and Vo are inconclusive.

In their latest study of the automultiplication reaction **1b** → **3b** without the intervention of physical or chemical chiral initiators, Soai *et al.*[40] discovered that the enantiomeric distribution ratio is strongly solvent-dependent: whereas reaction in toluene afforded results similar to those reported by Singleton and Vo, which the authors ascribed to "unknown chiral factors", the ratio was close to unity in an ether–toluene system. In 37 trials "using new and clean equipment", the results showed "an approximate stochastic distribution (19 times formation of *S* and 18 times *R*)". Evidently, for whatever reason, the ether-toluene environment served to "lessen the effect of unknown chiral factors". Thus, the results obtained in this solvent mixture are relatively clean-cut and do not suffer from the complications introduced by the presence of the putative chiral impurities in the work of Singleton and Vo.

While the enantiomeric ratios of **3b** obtained in this latest work by Soai's group do show "an approximate stochastic distribution", the number of runs is well below that required for a statistically significant set of trials. The question then arises: what would the distribution have been if, hypothetically, there had been thousands of runs – enough for the law of large numbers[41] to apply? In the absence of the requisite data, one is in no position to answer this question with complete confidence; inductive inferences and projections are inherently fallible because propositions about the observed are no reason to believe any proposition about the unobserved[42]. It is possible, nevertheless, to make an educated guess based on the limited information supplied in Soai's study[40]. One indicator is the almost ideal alternation of *R* and *S* configurations. Another is the distribution of enantiomers, which shows "an approximate stochastic distribution" not only for the whole set of 37 runs but also for various stages all along the way: for example, the first 14 runs consist of seven *R* and seven *S* enantiomers, and the first 20 runs of ten *R* and ten *S* enantiomers. Accordingly, the claim for "an approximate stochastic distribution" seems quite plausible.

As to what causes the "approximate stochastic distribution", Soai *et al.*[40] take it for granted that "the initial small imbalance of enantiomers in racemic mixtures [of **3b**] that arises from the reaction of achiral reactants [**1b** and diisopropylzinc] becomes overwhelming to afford a highly enantiomerically enriched product". To provide evidence for this claim

was, of course, what motivated the authors' experiments in the first place, and their results are indeed consistent with and supportive of their conjecture. Nevertheless, a pure conjecture is all that it is. There is no *direct* evidence whatsoever for the existence of "the initial small imbalance of enantiomers in racemic mixtures", nor for the configuration of the dominant enantiomers and the corresponding ee values. The authors' claim thus rests on the shaky grounds of an untested – and possibly untestable – assumption based on a statistical estimate. Nor will it do to invoke the principle of parsimony[43] or Einstein's plea for simplicity[44] because the most obvious explanation may not be the best: in the absence of evidence to the contrary, a variety of complex but possibly more correct explanations, especially in light of the dramatic but still unexplained solvent effect and the unknown role of undetected chiral impurities, cannot be conclusively ruled out. An unambiguous solution to the tantalizing problem of the connection between cause and effect in these experiments is therefore likely to elude us.

Nevertheless, this difficulty should not discourage us from answering the question posed in the title of this section with a resounding YES. The enormous power of Soai's automultiplication reaction leaves little doubt that if an enantiomeric excess as tiny as 10^{-5}% is sufficient to initiate the amplification[33r,36], then an ee even as small as 10^{-9}% is surely capable *in principle* of initiating a similar cascade leading to an optically active product. There is no reason to think that for chiral initiators a critical ee value exists, somewhere between 10^{-9} and 10^{-5}%, below which automultiplication can no longer take place.

We thus conclude that it is all but certain that the Soai reaction is capable of producing optically active compounds by an absolute asymmetric synthesis, starting from nominally achiral reagents free of chiral contaminants and run under achiral conditions, *e.g.*, without the intervention of chiral physical forces. It is a remarkable achievement.

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41. If the probability of an event E at each trial is p, then the probability that E will occur with a relative frequency that is close to p increases with the number of trials and approaches 1 as the number of trials becomes extremely large. In the present context, E is the generation of *R* or *S* enantiomers and $p = 0.5$.
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44. According to an aphorism attributed to Albert Einstein, "Alles sollte so einfach wie möglich gemacht werden, aber nicht einfacher" ["Everything should be made as simple as possible, but not simpler"]. See: Quadbeck-Seeger H.-J.: *Zwischen den Zeichen. Aphorismen über und aus Natur und Wissenschaft*, p. 71. VCH, Weinheim 1988.