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Reflections on spontaneous asymmetric synthesis by amplifying autocatalysis †

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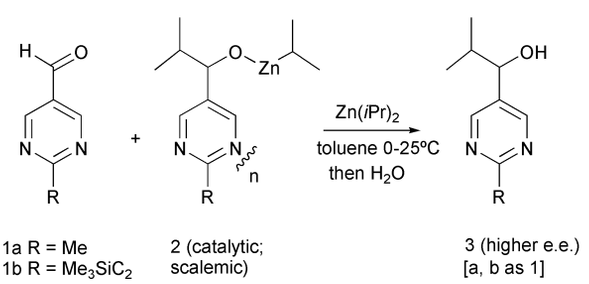
Spontaneous generation of chirality was observed in the course of studying the mechanism of asymmetric autocatalysis by NMR in ZnR_2 alkylation of pyrimidin-5-aldehydes. A systematic study was carried out in order to discover its origins. Even in clean fresh non-glass reaction vessels spontaneous ee was clearly observed, and was not dependent on any single reaction parameter. For comparison it was demonstrated that enantiomerically pure Zn alkoxide catalyst could control the configuration of the reaction product even when present at below micromolar concentrations. The high propensity of the Soai reaction system to produce an enantiomerically enriched product without initial bias is suggested to result from stochastic effects. These are especially important in autocatalysis because all the final products can be derived by breeding from a small number of initial events. The statistical excess of one enantiomer in that set is sufficient to generate a measurable ee in the product. The process is aided by the requirement for dimerisation before the product is an active catalyst. An enumeration that rationalises these observations is provided.

Introduction

Although Soai and co-workers reported the first example of amplifying enantioselective autocatalysis over seven years ago (Scheme 1),[1] some of the implications of the experimental demonstration of this long-sought phenomenon are only just being recognised. Among these is the potential for an autocatalytic reaction to result in spontaneous production of a single enantiomer of product. In fact, this outcome was realised by Soai and co-workers quite soon after the original publications, although their findings were presented in a Japanese patent that was neglected at the time and never published in the original literature.[2] This observation probably inspired their research on one of the most intriguing developments that arose from the initial observation. When the reaction of Scheme 1 is carried out without added zinc alkoxide, but in the presence of a number of enantiomerically pure substances in trace amounts, a high degree of autocatalytic amplification arises.[3] Homochiral crystals of sodium chlorate, or enantiomerically pure quartz crystals, can also initiate the autocatalytic formation of pyrimidinyl alcohol with high enantiomeric excess.[4] These findings have been quite extensively reviewed.[5]



Scheme 1 The basis of amplifying asymmetric autocatalysis.

† This is one of a number of contributions from the current members of the Dyson Perrins Laboratory to mark the end of almost 90 years of organic chemistry research in that building, as all its current academic staff move across South Parks Road to a new purpose-built laboratory.

The spontaneous generation of molecular asymmetry through a chemical reaction is almost unique in having generated an extensive literature, before any experimental demonstration. First Franks,[6] and Calvin[7] recognised that there were possible reaction schemes that could lead to autocatalytic amplification. The Franks model that has been widely quoted since 1953 is not easy to reduce to a chemical model, requiring "a chemical substance that is a catalyst for its own production and an anti-catalyst for the production of its own enantiomer". Calvin further emphasised the potential significance of stereospecific autocatalysis in molecular selection. These early papers stimulated much thought on the possible ways in which spontaneous autocatalysis might occur. Among several attempts to provide kinetic models for the process, Decker's suggestion that amplification can be achieved through a "quadratic model" that requires the regeneration of homochirality by a stereospecific reaction,[8] is highly relevant to the zinc-based autocatalysis:

$$A + (2R) \xrightarrow{k_a} 3R;\ A + (2S) \xrightarrow{k_a} 3S;$$
$$A + (S,R) \xrightarrow{k_b} 2S + R;\ k_a >>> k_b \quad (1)$$

A dimer model inspired by Kagan's analysis of non-linear effects, with preferential reactivity of a homochiral over the corresponding heterochiral complex, proved valuable to us in developing the mechanism in the Soai case of autocatalysis, as is discussed later.[9,10] It is presented, along with other kinetic models, in a lucid and very pertinent review by Goldanskii and Kuz'min.[11]

Recent interest in the spontaneous generation of asymmetry stems from a paper by Singleton and Vo.[12] Their results were similar to those reported by Soai previously in his patent, alluded to above, but were more extensive and subject to a specific interpretation – spontaneous generation of asymmetry is the consequence of chiral impurities, albeit below the level of detection. A response from Soai *et al.* indicated that stochastic

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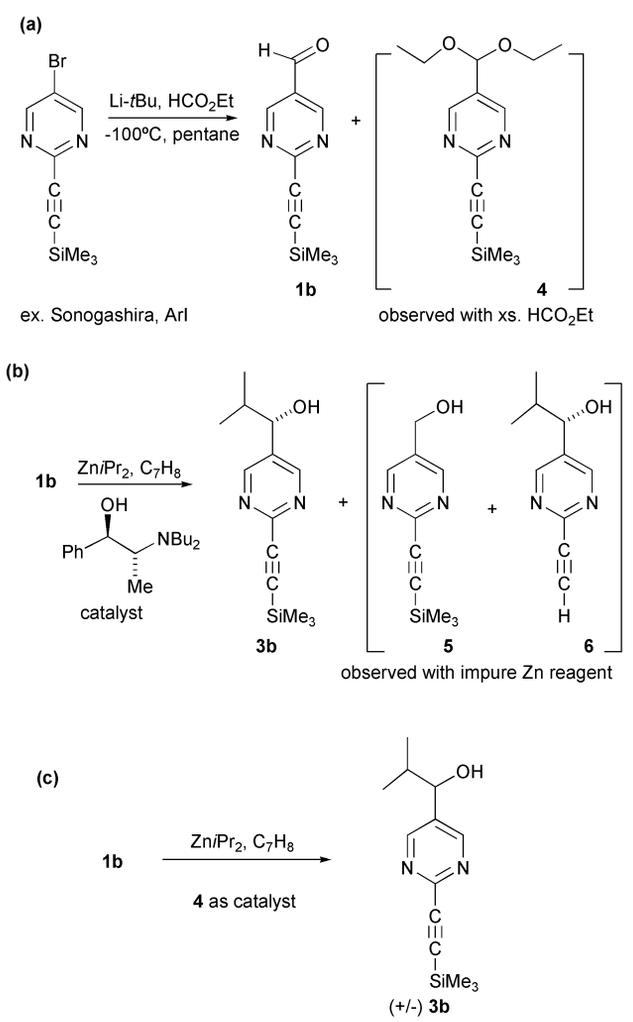
enantiomeric excess in the absence of catalyst could be consistently obtained by working in diethyl ether–toluene mixtures.[13] In a further publication, the same group demonstrated that significant levels of asymmetry can be obtained starting with vanishingly low levels of enantiomeric excess in the alcohol pre-catalyst.[14] From these observations the empirical basis is clear; there is a strong propensity for the reaction of pyrimidine-5-aldehydes with diisopropyl zinc to generate an enantiomerically enriched product, without there being a specifically planned asymmetric input (*i.e.* a chiral seed) into the reacting system.

These experiments do not offer a definitive insight, in the sense of an understanding of the origins of spontaneous asymmetry through autocatalysis. We present new observations and offer an interpretation, not requiring the presence of chiral impurities to seed the reaction.

Results and discussion

Experimental observations of spontaneous autocatalysis

In common with others working in the field, our studies on the mechanism of autocatalysis led to sporadic and rather random observations of spontaneous chirality generation. As a purely empirical observation, this occurred more readily when the alkynylpyrimidinal **1b** was employed. Soai's work has amply demonstrated the superior efficacy of this type of reactant. The reactant has been reported but since experimental details are lacking our methods are reported in detail here. The enantiomerically pure products were prepared by using a conventional catalyst (Scheme 2).



Scheme 2 Synthesis of the reactants employed in the work.

In order to generate a racemic product **3b** unambiguously, the achiral acetal **4** that was produced fortuitously in the synthesis of **1b** was employed as a catalyst in the synthesis. Since a main objective of our work was to define the mechanism of asymmetric autocatalysis through the NMR detection of reactive intermediates, catalytic experiments were carried out *in situ*. It was found that the background reaction, in the absence of added Zn alkoxide, occurred at a significant rate. In one early experiment, a deficiency of $Zn(i\text{Pr})_2$ was added to 0.35 M aldehyde **1b**, and the sample was observed by ^{1}H NMR until all the Zn reagent had been consumed, warming the sample from 233 K to 298 K. The NMR spectra showed the presence of unreacted aldehyde (integration gives an alkoxide : aldehyde ratio of 2.8 : 1). Since some precipitation was evident, a large excess of $Zn(i\text{Pr})_2$ was added, giving a clear solution.

The low field region of the ^{1}H NMR spectrum taken subsequently at 298 K indicated clearly that the solution contains alkoxide that is largely homochiral.[15] After workup, the sample of alcohol **3** was shown to have an ee of 84% (*R*) by chiral LC analysis. Many further NMR experiments were carried out with diverse outcomes, but in several cases a significant excess of homochiral product (enhanced intensity of the high-field signal in the aromatic region) was observed, and confirmed by polarimetry and chiral LC. The appearance of the aromatic region of the ^{1}H NMR spectrum in six different experiments after completion of the alkylation process but before any workup procedure is shown in Fig. 1.

During the course of a series of related NMR experiments in which product formation was monitored *vs.* time, it was observed that the rate of product formation was variable, but not in a predictable way. Indeed, no common factor could be identified that linked all of those experiments in which significant enantiomeric excess was generated. In some cases, a slow initial phase was succeeded by a phase of rapid consumption of the reactant aldehyde; in others, a more regular transformation was observed (Fig. 2). There appeared to be no formal correlation between these observations and the final enantiomeric purity of **3**. Nevertheless, the second of the two runs displayed an ee of 6% (*R*) on HPLC analysis, whilst the first gave a racemic product within experimental error.

In view of the surprising ease of formation of enantiomerically enriched products in reactions lacking an initial source of chirality, a sequence of runs was carried out *in vitro* to delineate the effect. At the same time, the attenuation of efficiency in asymmetric autocatalysis was examined as initial catalyst concentration was decreased. Standard conditions were adopted for all these runs. Taking first the catalyst-free systems, and following a single positive experiment in ether, a series of runs were carried out in batches over a period of two weeks; a majority were carried out in toluene but with some others in diethyl ether. As standard conditions, the mixture was stirred overnight at 273 K, and product isolated at the end of that period. As a general rule, the toluene runs appeared orange, albeit clear, whereas the ether runs showed substantial precipitation.[16] After workup, the samples were assayed using chiral LC. Because of the importance of accuracy in cases where the enantiomeric excess is small, a calibration sample of 3% ee (*R*) was prepared by mixing the hands of enantiomerically pure **3**. Four independent assays gave 1.5, 2.5, 3.8 and 5.5% ee, consistently with (*R*) in excess. It was concluded that results could be quoted with an accuracy of ± 2.5% All of the runs had been carried out in standard Schlenk tubes without any special effort to exclude trace impurities, and hence the effect of altering the vessel surface was investigated. A series of runs were carried out in glassware that had been previously treated with aqua regia, with the ensuing result of low enantiomeric excesses (2.5–16%) but with the (*S*)-enantiomer always dominant. To provide standards for comparison we were interested in the conventionally autocatalysed reaction in the same system – what are the limits below which the initial chiral Zn alkoxide seed is

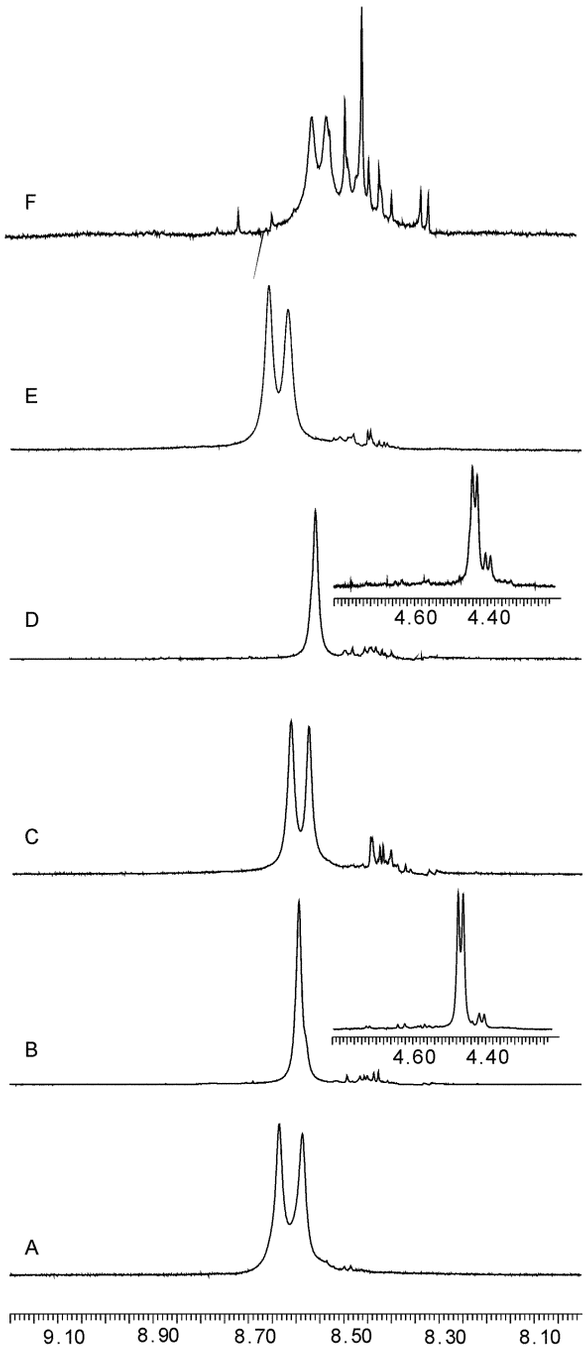


Fig. 1 The low-field region of the ^{1}H NMR spectrum at 298 K in six different experiments involving addition of Zn(*i*Pr)$_2$ to aldehyde **1b** in the absence of catalyst. **A** 0.35 M **1b**, 1.76 M [Zn] warmed from 233 K; **B** 0.35 M **1b**, 0.28 M [Zn] 203 K then excess [Zn], warmed to rt; **C** 0.26 M **1b**, 1.7 M [Zn], 298 K; **D** 0.26 M **1b**, 0.1 M [Zn] then excess [Zn], 298 K; **E** 0.26 M **1b**, 2.5 M [Zn], 298 K **F** 0.09 M **1b**, 0.16 M [Zn], 203 K then seq. addn. [Zn] before warming. C**H**OZn region inset in **B** and **D**.

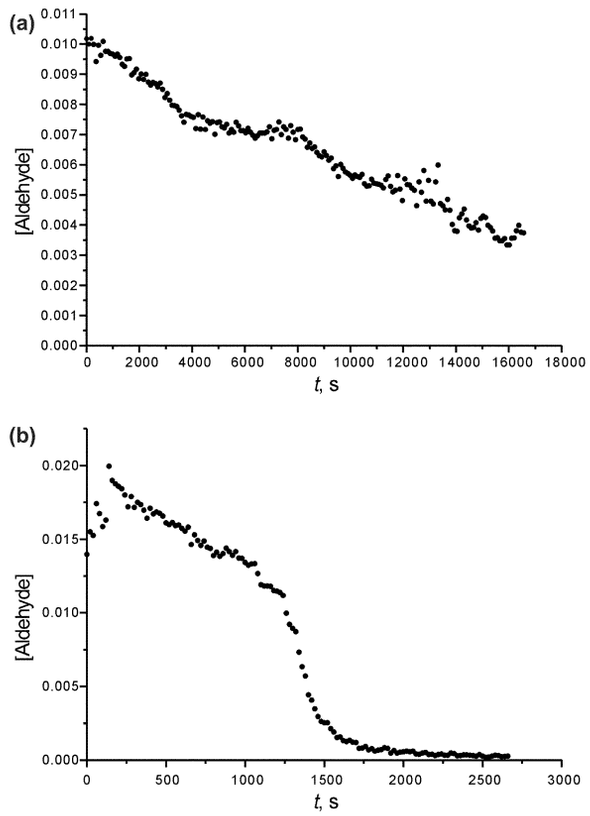


Fig. 2 Progress of the reaction between aldehyde **1b** and Zn(*i*Pr)$_2$ in C_7D_8 at 273 K. Product formation was monitored by integration of the ^{1}H NMR signal of aromatic protons of aldehyde against the signals of residual aromatic protons in the 4.5 ppm region. Starting concentrations: (a) 0.01 M **1b**, 0.02 M [Zn]; 300 4 K point spectra were taken at 60 s intervals. (b) 0.02 M **1b**, 0.04 M [Zn]; 140 4 K point spectra were taken at 20 s intervals.

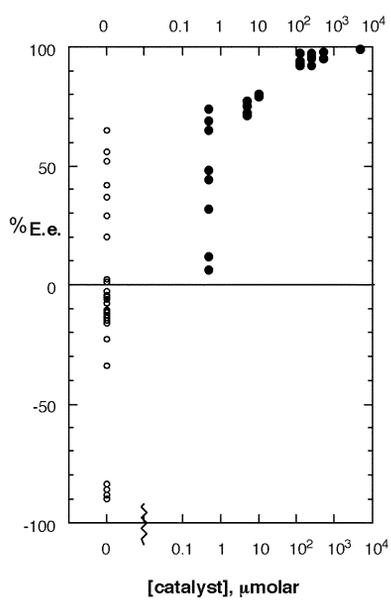


Fig. 3 Dependence of the ee on catalyst concentration for the reaction between **1b** (0.025 M) and Zn(*i*Pr)$_2$ (0.0425 M) in toluene (4 ml) at 273 K in the presence of 0.002 to 20 mol% catalyst (*R*)-**3b**. The $x = 0$ points refer to reactions without added catalyst from a variety of experiments described in the text, including *in situ* NMR.

ineffective in inducing amplification? Since essentially all the published work on asymmetric autocatalysis has been carried out in toluene or cumene, we were interested in defining the lower limit of the effect in toluene. Standard runs were carried out with 99% enantiomerically pure (*R*)-**3** as catalyst, 0.025 M aldehyde **1b** and 0.0425 M Zn(*i*Pr)$_2$. The catalyst proportion varied between 2 mol% and 0.002 mol%, and at the lowest concentration the solution was 0.5 micromolar in **3b**. The results obtained, shown in Fig. 3, demonstrate that there is a considerable range of concentrations over which asymmetric autocatalysis is sustained.

At 10 μmolar initial catalyst concentration or below, there is significant loss of enantiomeric purity in the product, although the same hand was obtained in all cases. The full set of catalyst-free runs is included for comparison, excluding the systematic data recorded in Fig. 4 below.

In order to provide a more systematic basis for these observations of spontaneous asymmetric synthesis, a further set of reactions was carried out. All of these adhered to the

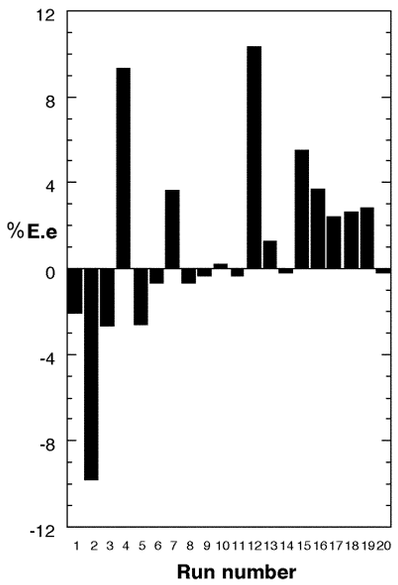


Fig. 4 A batch of samples of spontaneous autocatalytic reactions carried out in polycarbonate tubes by inverse addition of $Zn(iPr)_2$ to aldehyde **1b** in toluene at 0 °C; otherwise conditions as Fig. 3.

conditions described in the caption to Fig. 4. They were performed sequentially in new polycarbonate tubes and all the operations of mixing, reaction, quenching and analysis were completed in a single day. The results of HPLC analysis (Fig. 4) show a distribution in which both (*S*) and (*R*)-products feature. Since we feel it is important to demonstrate the outcome of single experiments rather than an augmented sequence, these are presented without further modifications. In understanding the significance of these results, it is important to note that the distribution of ee in a stochastically driven set is **not** expected to be 1 : 1 but follows the same probability laws as a coin-tossing sequence. In their recent paper, Soai and co-workers describe the results of 37 experiments conducted with aldehyde **1b** and $ZniPr_2$ in Et_2O, of which 18 resulted in (*R*)- product and 17 resulted in (*S*)-product, with a minimum ee of 15%.[17] In our case there are 20 experiments (the maximum number feasible in a single day's operation under our conditions) of which 8 resulted in (*R*)-product, 4 resulted in (*S*)-product and 8 were racemic within experimental error.

Given the non-linear amplification mechanism and the idealisations embodied in our model studies, one may not extract statistical information about the initial distribution of catalytic seeds directly from the chiral distribution of products. Our data consist of a monomodal product distribution; the mean value is slightly displaced from ee = 0%, and there is a high probability of obtaining the mean value in an experiment. Large fluctuations about the mean value were also observed, but with much lower frequency. The crucial qualitative feature of these data is that they indicate that the observed product distribution is generated by statistical fluctuations in a significant number of initial seeding events. The large fluctuation in the product ee is the signature of quite small statistical variations in the seed distribution that have been strongly amplified. The non-linear nature of the amplification mechanism investigated here is sufficiently powerful that it is able to convert the random statistical fluctuations about the racemic mean in a binomially distributed mixture of chiral molecules into a significant enantiomeric excess. Observation of a bimodal distribution, as has been reported by Kondepudi and Asakura,[5c] in spontaneous asymmetric crystallisation, is the signature of a bifurcation in which the outcome is determined by an avalanche, seeded by a single event. The product distributions they obtained in these crystallization studies are very narrow. This is because a single event triggers the complete consumption of reagents with essentially homochiral product before a second random triggering event of opposite chirality can occur. In contrast, Soai *et al.* obtained a rather broad, bimodal product distribution. The width of each distribution mode indicates that the outcome is unlikely to be caused by a single bifurcation event, so that these results appear not to have been produced by a single trigger. However, if we allow for many triggering events, that bimodal structure is rapidly lost.

Finally the effects were demonstrated on a preparative scale; aldehyde **1b** (165 mg) in dry toluene (9 ml) and $Zn(iPr)_2$ (440 mg) in dry toluene (9 ml) were mixed at −78 °C with stirring and then allowed to warm slowly to rt by removing the source of cooling. The reaction mixture changed from brown-red to scarlet to yellow. After stirring for a further 20 minutes at rt, the mixture was worked up conventionally and the product alcohol **3b** isolated and shown to have an ee of 52% (*R*) by chiral LC.

Taken together, these results demonstrate the capacity of an amplifying autocatalytic reaction to spontaneously generate an enantiomerically enriched product under a range of conditions with different scope from those reported by previous authors. The effect cannot be erased by conventional methods for the removal of adventitious contaminants. As Mislow has lucidly pointed out in his recent review of absolute asymmetric synthesis, the collective evidence indicates 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".[18]

Augmenting statistical enantiomeric excess

Why is the asymmetric autocatalytic reaction discovered by Soai so prone to generating spontaneous enantiomeric excess? Since further examples of the phenomenon are lacking, there are as yet no standards for comparison. The answer lies in a consideration of the processes by which the catalyst is initially formed and then propagated. In a process involving $2M$ unbiased trials involving two outcomes, x and y whose probabilities are, respectively, p and $(1 - p)$, the distribution function for n observations of x in the trial set is given by the binomial distribution of eqn. (2).

$$Pr(n) = [(2M)!/(n!(2M - n)!)]\, p^n(1 - p)^{2M - n} \qquad (2)$$

Any reaction that generates a chiral racemic product from achiral precursors, without asymmetric influences, will produce a product distribution of this type. There will be an excess of one enantiomer on a purely statistical basis, analogous to the excess of heads or tails in a coin-tossing sample.[19]

The classical statistical fluctuation in the enantiomer distribution that is characteristic of the binomial distribution offers a natural seeding mechanism for the subsequent amplification of chirality, without the invocation of external chiral perturbations such as circularly polarized photons, or physical advantage factors such as the influence of the parity-violating electroweak interaction. In the limit of large M, the binomial distribution may be approximated by a normal distribution, which for $p = 1/2$ has mean value $\mu = M$ and a standard deviation $\sigma = \sqrt{M}/2$ that provides a measure of the likely statistical fluctuations in the sample. The probability of obtaining a pure racemic mixture of R and S as the product of an unbiased chemical reaction is consequently small; in a series of identical trials the maximum value of the normalized distribution varies as $\sqrt{M}$ and its effective width varies as $1/\sqrt{M}$.

When the reaction pool is in the millimolar range, this distribution width corresponds to an enantiomeric excess in the region of 2.75×10^{-9}%. This clearly is not significant, and for statistical factors to play a part in the spontaneous generation of ee, a far smaller pool is required. In order to obtain an

enantiomeric excess in a chemical reaction of laboratory scale, it is not sufficient that this statistical fluctuation simply generates an initial composition with a large number of one type of enantiomer in excess. Goldanskii and Kuz'min[10] identify the critical parameter as the chiral polarization, η, given in eqn. (3):

$$\eta = [n(R) - n(S)]/[n(R) + n(S)] \qquad (3)$$

where $n(R)$ and $n(S)$ are, respectively, the number of R- and S-enantiomers so that η provides a direct measure of the relative fluctuation from the mean (racemic) configuration, for which $n(R) = n(S) = M$, and $n(R) + n(S) = 2M$.

The parameter η is equivalent to enantiomeric excess in a bulk sample. In the absence of any external bias or advantage factor, a random statistical fluctuation in the distribution of *R* and *S* will lead to a significant value of η only for values of *M* that are very small compared to Avogadro's number. In order to generate significant amounts of enantioenriched product on laboratory timescales, the need for this statistical fluctuation to propagate with increasing $|\eta|$ from a value close to $\eta = 0$ must be balanced against the competition with other chemical reactions involving the reagent pool. In order to generate a significant deviation from $\eta = 0$, $n(R) + n(S)$ must be small, but not so small as to be negated by a subsequent random fluctuation, or by a dominant racemizing reaction that acts in competition with a chiral amplification mechanism.

We are already aware from both kinetic studies and physicochemical measurements on the Zn alkoxide **2** in solution, that it behaves as a dimer for which the racemic and enantiopure forms are present at comparable concentrations. The kinetics indicate that the catalytic species itself contains two molecules of alkoxide, and the simplest interpretation is that the observed dimer is the true catalyst.[20] Consider then, the initial phases of the spontaneous reaction, where the concentration of active catalyst is extremely low. Sporadic direct addition reactions may occur in the bulk solution or at surfaces. This provides an initial pool of zinc alkoxide product, but cannot by itself instantly generate an autocatalytic reaction, because dimerisation needs to take place first. NMR line-shape analysis demonstrates that the half-life of individual dimers is significant in the normal temperature range of autocatalysis, extrapolating to around 30 seconds at 273 K (*i.e.* $k_{diss} = ca.\ 0.025\ s^{-1}$). Making a guess of $10^5\ M^{-1}\ s^{-1}$ for the rate constant of monomer association, this points to an association constant for dimerisation in the region of $4 \times 10^6\ M^{-1}$. This provides an effective mechanism for limiting the number of initial events that trigger autocatalysis. In turn, it provides a small pool of product available for further autocatalytic events that will possess a statistically significant bias towards one enantiomer. The qualitative thrust of the argument is clear; the mechanism of autocatalysis revealed by our previous studies severely constrains the number of molecular events than can initiate the spontaneous process, since the true catalytic species is only accessible indirectly. Hence the statistical enantiomeric excess, relevant to the spontaneous generation of chirality, is far higher than that calculated from the number of molecules of catalyst involved in the reaction overall. We do not know, of course, how many initiation events are involved in reactions on a typical scale that involve the production of 100 μmoles (6×10^{19} molecules) of product, but the above discussion indicates that it is likely to be a small fraction of the total catalytic productivity. This is reinforced on two counts: Soai's work at very low catalyst ee and high loadings, and the results described here at high catalyst ee and very low loadings both indicate the scale of amplification possible.

General consideration of the kinetic conditions under which spontaneous autocatalytic generation of enantiomeric excess may occur have been presented by Goldanskii and Kuz'min.[10] We review their conclusions here in the context of the present study, because they provide some insight into the special conjunction of circumstances that are necessary to lead to spontaneous chiral amplification. The essential requirement for chiral enhancement is that of a "bifurcation" of the racemic state reflecting an intrinsic instability of the mean configuration. This could be induced either by introducing an antagonism (or annihilation) of chiral entities to form achiral products (*c.f.* Frank), or an autocatalytic stereospecific reaction that can be reduced in simplest form to an effective trimolecular concurrence of the form $A + 2R \longrightarrow 3R$ or $A + 2S \longrightarrow 3S$, where *A* is an achiral substrate(s). It is sufficient that reactions that occur in practice may be reduced to this effective form; they may involve a complex set of intermediate steps.

The essential feature of this form of autocatalytic trimolecular concurrence reaction, or "superautocatalysis", is that the differential equation that determines $\eta(t)$ depends non-linearly on the enantiomeric excess. The variation of $\eta(t)$ assumes the characteristic form of eqn. (4):[10]

$$\frac{d\eta}{dt} \alpha(\theta)\eta - \beta(\theta)\eta^3 \qquad (4)$$

where θ is a function of the process rate constants and reagent activity involved in the autocatalytic reaction, and $\alpha(\theta)$ and $\beta(\theta)$ are functions depending both on the details of the reaction and on θ. Non-linear equations of this type are also characteristic of non-equilibrium phase transitions, with the observed behaviour determined by the ratio α/β. The racemic state is stable for $\alpha/\beta < 0$ and reaches the critical bifurcation point at $\alpha/\beta = 0$. If $\alpha/\beta > 0$, spontaneous mirror symmetry breaking takes place, and any enantiomeric excess existing initially in the system will undergo non-linear amplification towards the chirally polarized limits $\eta = \pm 1$. In the homochiral dimer-catalyzed model, the reactions corresponding to the "superautocatalysis" step,[10] may be written in the form:[9]

$$\begin{aligned} RR + A + Z &\longrightarrow RR + RZ \\ SS + A + Z &\longrightarrow SS + SZ \end{aligned} \qquad (5)$$

where *RR* and *SS* denote homochiral dimers of the zinc complexes *RZ*, and *SZ*, and *A* and *Z* the achiral substrates. The zinc complexes rapidly generate an unbiased distribution of dimers, regenerating the stereospecific catalysts *RR*, and *SS*, together with the catalytically inert *RS*≡SR.

This pair of reactions conforms to the "trimolecular concurrence" criterion identified by Goldanskii and Kuz'min as the essential ingredient of non-linear bifurcation. If the effective rate constants $\alpha(\theta)$ and $\beta(\theta)$ are both positive under the prevailing reaction conditions, a small enantiomeric excess of the distribution of zinc complexes will be amplified, preferentially regenerating the active catalysts *RR* or *SS*. In principle, any fluctuation will result in a bifurcation in the model system; in practice, the statistical fluctuation must be sustained for sufficient time that it is not overwhelmed by a subsequent fluctuation of opposite enantiomeric excess, or by any other competing processes in the system.

The practical question of the feasibility of this mechanism then centres on the values of the rate constants involved in the various reaction pathways, the values of reagent concentrations that lead to $\alpha(\theta)/\beta(\theta) > 0$, as well as the minimal deviation from $\eta = 0$ that will lead to spontaneous enantiomeric excess. Conditions suitable for chiral amplification are not characterized solely by a formal chemical mechanism, because they depend also on the details of composition of the system. The available experimental evidence and the results of model kinetic studies indicate that for the reaction conditions under investigation, the racemic state is in the critical regime of the parameters $\alpha(\theta)$ and $\beta(\theta)$ and that a very small enantiomeric excess of order $\eta = \pm 0.0001$ with respect to the active catalyst is sufficient to

propagate a large enantiomeric excess on a laboratory timescale. This is illustrated in Fig. 5, based on the concentrations of the main experiments in Fig. 3, and allowing for a single burst of a billion spontaneous initiation events in a 100 $\mu\mu^3$ domain. All the aldehyde in that domain is then consumed. At that stage the alkoxide has acquired a significant enantiomeric excess, such that its dissipation through the reaction medium ensures a very high enantioselectivity in the final product. If the timescale for catalyst doubling is of the order of $10–10^2$ seconds, feasible on the basis of earlier studies with the less reactive **1a**,[9] the overall time required to generate product on a macroscopic scale is reasonable.[21] Adoption of the tetrameric transition state ($[ZnOR]_2$ plus 2A·Zn complexes) recently proposed by Buono and Blackmond,[22] would not alter the conclusions.

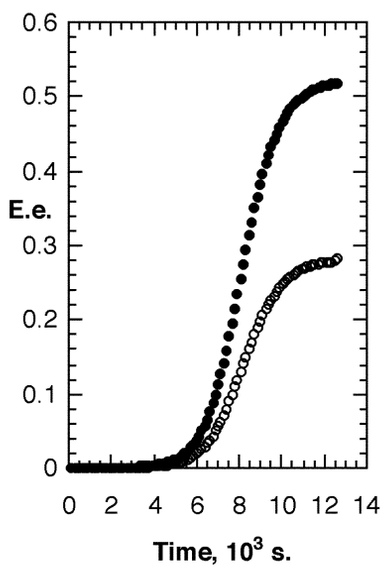


Fig. 5 Amplification of statistical ee from a sample of 10^9 molecules of racemic product **2** formed in a domain of 100 $\mu\mu^3$. Initial conditions: [**1b**] 0.025 M, [Zn(*i*Pr)$_2$] 0.04 M, kinetic model as text. Filled circles = dimer, open circles = monomer; consumption of **1b** is essentially complete.

Summary and conclusions

Asymmetric alkylations by organozinc reagents are known to be susceptible to strong positive non-linear effects, and there are probably more examples here than in any other chemical process.[12] The reaction is readily catalysed, not only by organozinc alkoxide chelates but by a significant range of metal-based Lewis acids.[23] In the Soai case, a substantial range of molecular triggers can initiate autocatalysis. Once established, the reaction product, or a closely related species, is the probable vector of autocatalytic turnover. Taking all these factors into consideration, it is not surprising that the sole case of amplifying asymmetric autocatalysis recorded to date arises from this reaction. Even so there are severe restraints – the reaction is unique to diisopropyl zinc, and all the effective reactants are rigid aromatic γ-aminoaldehydes. This set of factors provides circumstantial evidence that it will be a rare occurrence in organic catalysis, and not general. It does not preclude the existence of other undiscovered examples, but rationalises their apparent elusiveness.

The origin of biological chirality has generated an enormous literature in which both physical and chemical processes have been widely canvassed as possibilities.[24] Many authors have drawn attention to the potential of asymmetric autocatalysis to provide a pool of non-racemic molecules of potential metabolites under prebiotic conditions, and hence play an important part in the induction of chirality in the natural world. Because the autocatalytic model provides a sustaining influence since the initial enantiomer bias is indelibly augmented, there are attractive features in this model. Of course many alternatives have been discussed, and an autocatalytic process seems a significantly better candidate than *e.g.* the miniscule energy differences arising from the non-conservation of parity in the weak nuclear interaction, even when taken in tandem with initiation processes dependent on the circular polarisation of incident radiation.[25] But enantiomer enrichment by crystallisation is a far better candidate still, simply because it is a relatively commonplace phenomenon.[5c] In propagating autocatalysis, each initial seed must traverse sufficient space to make contact with new substrate and reagent. The analogy with the nucleation process in crystallisation is clear, since both depend on local effects in a small volume of a liquid medium that are then efficiently dispersed through the bulk sample. In contrast to the single example of amplifying autocatalysis described here, there are many examples of spontaneous enantiomer generation through crystallisation, or ordered phase separation.[26] Although amplifying autocatalysis is the most elegant and chemically attractive option for the origin of biochirality, its apparent rarity may define the probability of its involvement in prebiotic chemistry.

Finally, we observe that familiar chemical processes are deterministic, because a very large number of events are involved at the molecular level. Stochastic behaviour is far more commonplace in, and perhaps even central to the working of biology.[27] In this respect, the spontaneous amplification of chirality in the Soai reaction by stochastic mechanisms that require a small original pool of seed molecules, sufficient to possess a significant statistical enantiomeric excess, forms a bridge between the familiar territories of chemists and biologists.

Experimental section

Techniques, materials and instrumentation

Reactions involving air-sensitive materials were carried out under a dry argon atmosphere using standard vacuum-line techniques in flame-dried Schlenk glassware.

Mass spectra were carried out on a Micromass Platform 1 APCI system.

Exact masses were measured using a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer operating at a resolution of 5000 (full-width half-height). Positive ion spectra were calibrated relative to PEG with tetraoctylammonium bromide as the internal lock mass. Negative ion spectra were calibrated relative to poly-DL-valine with leucine enkephalin as the internal lock mass.

Chiral gas chromatography measurements were recorded on a Chrompack CP9001 using CP-Chiracel DEXCD 25m, 0.25mm internal capillary. Standard conditions used were 100 °C oven temperature heating to 150 °C at a rate of 0.7 °C per minute and a flow rate of 1 ml per minute, He carrier.

HPLC measurements were carried out on a Gilson HPLC (Manometric unit and mixing chamber type: 805, pump type: 306, loop 20 μl) using a chiral Chiracel-OD column. The standard conditions used were 97% cyclohexane and 3% isopropanol mobile phase at a flow rate of 1 ml per minute. All solvents were degassed with helium for 30 min before use.

^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200 (200 MHz), Bruker DPX200 (200 MHz), Bruker DPX250 (250 MHz), Bruker DQX400 (400 MHz) or Bruker AMX500 (500 MHz) spectrometers.

Infrared spectra were recorded on a Perkin Elmer 1750 FT spectrometer.

Synthesis of Zn(*i*Pr)$_2$.[28] $ZnBr_2$ (48 g, 0.213 mol) was dried intensively for 3 h at 100 °C *in vacuo*. After cooling down to room temperature dry diethyl ether (20 ml) was added against a

stream of argon and the reaction vessel cooled to 5 °C on a water bath. Then an *i*PrMgCl solution (200 ml of a 2 M solution, 0.4 mol) was added in portions *via* syringe and the mixture stirred at room temperature for 12 h under argon. The suspension was filtered under argon and the grey residue washed with dry pentane (8 × 10 ml). The volume of the filtrate was reduced *in vacuo* (35 mm Hg) and the remaining black liquid transferred to a flame-dried distillation apparatus where it was distilled *in vacuo* to yield the desired compound as a colourless liquid (21 g, 70% yield). Bp 52 °C/60 mm Hg, blackening slowly on exposure to light. δ_H (400 MHz, C_7D_8) 0.67 (1H, septet, C-*H*, *J* = 7.9 Hz), 1.24 (6H, d, CH_3, *J* = 7.9 Hz); δ_C (100.6 MHz, C_7D_8) 18.65 (*C*-H), 21.66 (2 *C*H_3).

2-(Trimethylsilyl)alkynylpyrimidyl-5-carbaldehyde, 1b.[29] Following a general procedure by Rho and Abuh,[30] 5-bromo-2-iodopyrimidine (18.55 g, 65.1 mmol), CuI (0.169 g, 0.08 mmol) and $Pd(PPh_3)_4$ (0.562 g, 0.485 mmol) were suspended in di*iso*propylamine (112 ml) under argon and cooled to 0 °C. Against a flow of argon, a solution of trimethylsilylacetylene (6.38 g. 65.1 mmol) in di*iso*propylamine (56 ml) was added slowly over 3 h. After the addition was complete, the mixture was stirred for an additional hour at 0 °C and then allowed to warm to room temperature. The residues were filtered off under argon and the solvent was removed *in vacuo*. The pale brown crude product was sublimed *in vacuo* at 120 °C to yield *3-bromo-5-(trimethylsilyl)alkynylpyrimidine* as a white solid (15.4 g, 91.6% yield). δ_H (200 MHz, $CDCl_3$) 0.28 (9H, s, Si(CH_3)$_3$), 8.75 (2H, s, Ar-*H*); δ_C (50.3 MHz, $CDCl_3$) −0.60 (Si(*C*H_3)$_3$), 96.23 (*C*≡), 101.33 (Si–*C*≡), [119.56 (*C*–C≡), 150.26 (*C*–Br), 157.91 (2 *C*H)] (aromatic *C*); *m*/*z* (APCI$^+$) = 258.07. Under an argon atmosphere 3-bromo-5-(trimethylsilyl)alkynylpyrimidine (5 g, 19.5 mmol) was dissolved in dry diethyl ether (250 ml). The mixture was cooled to −100 °C and ^{t}BuLi (11.75 ml of a 1.7 M pentane solution, 20 mmol) was slowly added against a stream of argon and under vigorous stirring. After 30 min stirring at −100 °C, ethyl formate (1.475 g, 20 mmol) was added slowly *via* syringe. After a further 30 min of stirring at −100 °C, the mixture was quenched with ethereal HCl (10 ml of a 2 M solution) and allowed to warm to room temperature. The yellow mixture was poured into water (50 ml) and extracted with $CHCl_3$ (5 × 40 ml). The combined organic phases were dried over Na_2CO_3 and the solvent removed *in vacuo* to yield a red-brown oil (4.1 g). The crude product was purified by chromatography on silica gel (eluent pentane–acetone 4 : 1) and the orange solid recrystallised from hexane to yield **13** as white crystals (1.3 g, mp 96–97 °C, 33% yield). Additional purification was achieved by sublimation *in vacuo*. δ_H (500 MHz, $CDCl_3$) 0.38 (9H, s, Si(CH_3)$_3$), 9.17 (2H, s, Ar–*H*), 10.16 (1H, s, C*H*O); δ_C (125.8 MHz, $CDCl_3$) −0.25 (Si(*C*H_3)$_3$), 100.23 (*C*≡), 102.33 (Si–*C*≡), [127.06 (*C*–C≡), 155.76 (*C*–CHO), 158.66 (2 *C*H)] (aromatic *C*), 188.57 (*C*HO); *m*/*z* (APCI$^+$) = 204.25.

2-(Trimethylsilyl)alkynylpyrimidyl-5-carbaldehydediethyl acetal, 4. The synthesis was similar to that described for 2-(trimethylsilyl)alkynylpyrimidyl-5-carbaldehyde, but with a 2-fold excess of ethyl formate. A 1 : 1 mixture of acetal and the respective aldehyde was obtained, which was separated by chromatography (SiO_2, eluent pentane–acetone 4 : 1). The oily liquid, from the fractions containing acetal, was purified by Kugelrohr-distillation (160 °C, 0.5 mm Hg, yield: 45%). δ_H (200 MHz, $CDCl_3$) 0.15 (9H, s, Si(CH_3)$_3$), 1.11 (6H, t, 2 CH_3, *J* = 7 Hz), 3.45 (4H, dq, 2CH_2, *J* = 7 Hz), 5.50 (1H, br s, C*H*OH), 8.62 (2H, s, Ar–*H*); δ_C (50.3 MHz, $CDCl_3$) −0.83 (Si(*C*H_3)$_3$), 14.79 (2 CH_3), 61.16 (2 CH_2), 94.31 (*C*≡), 97.84 (*C*HO_2Et), 102.33 (Si–*C*≡), [131.02 (*C*–C≡), 152.26 (*C*–CHO_2Et), 156.12 (2 *C*H)] (aromatic *C*); υ_{max} (NaCl disc) 2974, 2897 (C–H), 1114, 1059 (C–O), 1250, 874 (Si–CH_3); *m*/*z* (APCI$^+$) = 278.76; HRMS 279.1527 (calc for $C_{14}H_{23}N_2O_2Si$ = 279.1529).

(*S*)-2-Methyl-1-[2-(trimethylsilyl)alkynylpyrimidin-5-yl]propanol 3b. Zn(*i*Pr)$_2$ (400 mg, 2.6 mmol) was dissolved in dry toluene (10 ml) under an argon atmosphere. The solution was cooled to 0 °C and (−)*N,N*-dibutylnorephedrine (40 mg, 0.15 mmol) was added against a flow of argon. After the mixture was stirred for 30 min, a solution of aldehyde **1b** (150 mg, 0.75 mmol) was added dropwise within 1 h. The orange mixture was stirred for one additional hour at 0 °C and was then quenched with aqueous HCl solution (1 M, 2 ml). The organic phase was separated and the colourless aqueous layer neutralised with solid Na_2CO_3 (2 g) and extracted with diethyl ether (4 × 12 ml). The combined organic layers were dried over Na_2CO_3 and the solvent was removed *in vacuo*. The remaining orange solid was purified by chromatography (SiO_2, eluent pentane–acetone 8 : 1) to yield (*S*)-**3b** as white crystals (148 mg, mp 111–112 °C, 81% yield). The other enantiomer was obtained by a similar procedure using (+)*N,N*-dibutylnorephedrine as the catalyst ($[a]_D^{25}$ = 31.5 (*c* = 1, $CHCl_3$)). δ_H (500 MHz, $CDCl_3$) 0.30 (9H, s, Si(CH_3)$_3$), 0.89 (3H, d, CH–CH_3, *J* = 7 Hz), 0.96 (3H, d, CH–CH_3, *J* = 7 Hz), 1.99 (1H, dhep, C*H*, *J* = 7 Hz), 4.53 (1H, dd, C*H*OH, *J* = 7 Hz, *J* = 2.8 Hz), 8.64 (2H, s, Ar–*H*); δ_C (125.8 MHz, $CDCl_3$) 1.52 (Si(*C*H_3)$_3$), 17.77 (CH–*C*H_3), 18.29 (CH–*C*H_3), 35.66 (*C*H), 75.64 (*C*HOH), 94.71 (Si–*C*≡), 102.64 (*C*≡), [135.45 (*C*–CHOH), 151.80 (*C*–C≡), 156.07 (2 *C*H)] (aromatic *C*); *m*/*z* (APCI$^+$) = 248.55. Occasionally the corresponding primary alcohol *1-[2-(trimethylsilyl)alkynylpyrimidin-5-yl]methanol* **5** was observed as a side product. δ_H (500 MHz, $CDCl_3$) 0.30 (9H, s, Si(CH_3)$_3$), 4.79 (2H, s, CH_2OH), 8.72 (2H, s, Ar–*H*); δ_C (125.8 MHz, $CDCl_3$) −0.04 (Si(*C*H_3)$_3$), 60.72 (*C*H_2OH), 94.90 (*C*≡), 102.59 (Si–*C*≡), [132.85 (*C*–C≡), 152.03 (*C*–CHO), 156.37 (2 *C*H)] (aromatic *C*); *m*/*z* (APCI$^+$) = 206.02.

Another occasional side product was *(S)-2-methyl-1-[2-alkynylpyrimidin-5-yl]propanol* **6**; δ_H (250 MHz, $CDCl_3$) 3.14 (1H, s, *H*–C≡), 0.90 (3H, d, CH–CH_3, *J* = 7 Hz), 0.97 (3H, d, CH–CH_3, *J* = 7 Hz), 1.99 (1H, m, C*H*), 4.56 (1H, br d, C*H*OH, *J* = 7 Hz), 8.67 (2H, s, Ar–*H*); δ_C (62.9 MHz, $CDCl_3$) 17.73 (CH–*C*H_3), 18.83 (CH–*C*H_3), 35.60 (*C*H), 75.46 (*C*HOH), 76.26 (H–*C*≡), 81.99 (Si–*C*≡), [136.11 (*C*–C≡), 151.21 (*C*–CHOH), 156.14 (2 *C*H)] (aromatic *C*); υ_{max} (NaCl) 3430 (O-H), 2117 (C≡C), 1645 (C=N); *m*/*z* (APCI$^+$) = 176.73; HRMS 177.1030 (calc for $C_{10}H_{13}N_2O$ = 177.1028). Formation of both side products was avoided by re-distilling Zn(*i*Pr)$_2$ before use.

Synthesis of (±)-2-methyl-1-[2-(trimethylsilyl)alkynylpyrimidin-5-yl]propanol. Zn(*i*Pr)$_2$ (27 mg, 0.17 mmol) was dissolved in dry toluene (4 ml) under an argon atmosphere. The solution was cooled to 0 °C and acetal **4** (5.5 mg, 0.02 mmol) was added against a flow of argon. After the mixture was stirred for 30 min, a solution of aldehyde **1b** (20.4 mg, 0.1 mmol) was added dropwise within 1 h. The orange mixture was stirred for an additional hour at 0 °C and was then quenched with aqueous HCl solution (1 M, 2 ml).

The organic phase was separated and the colourless aqueous layer neutralised with solid Na_2CO_3 (1 g) and extracted with diethyl ether (4 × 8 ml). The combined organic layers were dried over Na_2CO_3 and the solvent was removed *in vacuo*. The remaining orange oil was purified by chromatography (SiO_2, eluent pentane–acetone 8 : 1) to yield (±)-**3b** as a colourless oil (20.1 mg, 81% yield) [mp of (±)-**3b** prepared from enantiopure material, 105–107 °C]. δ_H (500 MHz, $CDCl_3$) 0.30 (9H, s, Si(CH_3)$_3$), 0.89 (3H, d, CH–CH_3, *J* = 7 Hz), 0.96 (3H, d, CH–CH_3, *J* = 7 Hz), 1.99 (1H, m, C*H*, *J* = 7 Hz), 4.53 (1H, dd, C*H*OH, *J* = 7 Hz), 8.64 (2H, s, Ar–*H*); δ_C (125.8 MHz, $CDCl_3$) 1.52 (Si(*C*H_3)$_3$), 17.77 (CH–*C*H_3), 18.29 (CH–*C*H_3), 35.66 (*C*H), 75.64 (*C*HOH), 94.71 (Si–*C*≡), 102.64 (*C*≡), [135.45 (*C*–CHOH), 151.80 (*C*–C≡), 156.07 (2 *C*H)] (aromatic *C*); *m*/*z* (APCI$^+$) = 248.55.

Autocatalytic alkylation of 2-(trimethylsilyl)alkynylpyrimidyl-5-carbaldehyde 1b with Zn(*i*Pr)$_2$ and test on amplification of ee. Zn(*i*Pr)$_2$ (0.17 mmol) was weighed into a flame dried Schlenk tube which was flushed with argon. Dry toluene (0.25 ml) was added against a stream of argon *via* syringe and the solution cooled to 0 °C and stirred. Low ee (*S*)-2-methyl-1-[2-(trimethylsilyl)alkynylpyrimidin-5-yl]propanol **3b** was added as a solution in dry toluene (0.02 mmol in 1.75 ml of solvent) and the green to yellow mixture was stirred for 30 min in an ice bath. 2-(Trimethylsilyl)alkynylpyrimidyl-5-carbaldehyde **1b** was added slowly as a solution in toluene (0.1 mmol in 2 ml of solvent) over 1 h. The intense orange solution was stirred at 0 °C over night and showed precipitation the next day. The reaction was quenched with aqueous HCl solution (1 M, 2 ml); the organic phase was separated and the colourless aqueous layer neutralised with solid Na_2CO_3 (2 g) and extracted with diethyl ether (4 × 12 ml). The combined organic layers were dried over Na_2CO_3 and the solvent removed *in vacuo*. The remaining orange solid was 99% pure product (determined by NMR) and was subjected to chiral HPLC for determination of ee. All entries were derived from experiments performed similarly.

Heterogeneity tests. Three experiments were carried out in parallel to elucidate the role of precipitation in autoamplification (Exp. **A**, **B** and **C**). Zn(*i*Pr)$_2$ (0.17 mmol) was weighed in a flame dried glass vessel which was flushed with argon and equipped with a septum. Dry toluene (0.25 ml) was added against a flow of argon *via* syringe and stirred at room temperature. Low ee (*S*)-2-methyl-1-[2-(trimethylsilyl)alkynylpyrimidin-5-yl]propanol **3b** was added as a solution in dry toluene (0.02 mmol in 1.75 ml of solvent) and the green to yellow mixture was stirred for 30 min.

For experiment **A**, 2-(trimethylsilyl)alkynylpyrimidyl-5-carbaldehyde was added rapidly as a solution in toluene at room temperature (0.1 mmol in 2 ml of solvent) under efficient stirring.

For sample **B** stirring was stopped immediately after addition of the aldehyde solution.

Sample **C** was centrifuged at 2,500 rpm immediately after addition of a solution of aldehyde **1b**.

All three samples were quenched after 26 min with aqueous HCl solution (1 M, 2 ml), worked up as described above and analysed by HPLC.

Spontaneous autoamplification. Racemic 2-methyl-1-[2-(trimethylsilyl)alkynylpyrimidin-5-yl]propanol could be obtained when the respective aldehyde was reacted with Zn(*i*Pr)$_2$ in the absence of catalyst **3b**. A set of experiments was carried out using toluene and another series using diethyl ether as a solvent.

Zn(*i*Pr)$_2$ (0.17 mmol) was weighed in a flame dried Schlenk tube which was flushed with argon and equipped with a septum. Dry solvent (2 ml) was added against a stream of argon *via* syringe and stirred at room temperature. Aldehyde **1b** was added as a solution (20.4 mg, 0.1 mmol, in 2 ml of the respective solvent) in one injection under efficient stirring and the reaction stirred overnight at 0 °C. The next morning, all samples from diethyl ether showed substantial white precipitation while all samples from toluene were found to be clear orange solutions. Quenching and workup were performed as described above.

Low catalyst concentration assays. For the autocatalytic (*S*)-2-methyl-1-[2-(trimethylsilyl)alkynylpyrimidin-5-yl]propanol system, the concentration of autocatalyst **3b** [99% ee (+)] was decreased in a series of experiments with 0.1 mmol ml^{-1} of aldehyde from 5 mM down to 0.5 μM.

All other parameters remained unchanged, using Zn(*i*Pr)$_2$ (25.8 mg, 0.17 mmol) in toluene (0.25 ml) and the respective amount of autocatalyst dissolved in toluene (1.75 ml). Aldehyde **1b** was added as a solution (20.4 mg, 0.1 mmol, in 2 ml toluene) in one injection and the reaction stirred over night at 0 °C. Quenching and workup were performed as before.

Spontaneous autoinduction. This series of experiments was carried out with an inverse addition of Zn(*i*Pr)$_2$ to aldehyde **1b** in the absence of catalyst. To minimise the possibility of catalysis induced by any chiral admixtures, all reactions were carried out in disposable polycarbon test tubes.

2-(Trimethylsilyl)alkynylpyrimidyl-5-carbaldehyde **1b** used was purified by sublimation directly before use and stored under argon to avoid oxidation. Aldehyde (20.4 mg, 0.1 mmol) was placed in a plastic test tube equipped with a septum, covered with argon, dissolved in dry toluene (2 ml) and cooled to 0 °C. A solution of Zn(*i*Pr)$_2$ (25.8 mg; 0.17 mmol in 2 ml of toluene) was added *via* syringe in one rapid injection under vigorous stirring. The orange mixture was stirred for 30 min on ice and was quenched and worked up as described before. Samples were analysed by chiral HPLC in order to determine ee. In order to determine the error range of HPLC for determination of small ee, a sample of **3b** with an ee of 3% was prepared by mixing enantiomers of known high ee. The 3% ee (+) sample was measured four times, giving results of 1.5% ee (+), 2.5% ee (+), 3.8% ee (+) and 5.5% ee (+). An additional control of accuracy of integration was done by weighing printed and cut-out HPLC traces. This was done for four samples in a range of 5–10% ee (−) to 5–10% ee (+). All traces were weighed several times on an analytical balance. All calculated ees by weight were within a 3% error range; therefore a maximum error rate of ±3% ee was anticipated.

Kinetic measurements for spontaneous autoamplification. In a typical experiment, aldehyde **1b** (4 mg, 19.6 mmol) was weighed in an NMR-tube, covered by an argon atmosphere and was dissolved in deuterated toluene (0.35 ml). The sample was cooled to −78 °C and closed with a septum. Immediately before insertion of the NMR tube into the NMR machine (500 MHz), a solution of Zn(*i*Pr)$_2$ was added (2 equivalents, 0.30 ml of a 0.13 M solution in deuterated toluene) *via* syringe. With intervals varying between 10 and 30 seconds according to the experiment, 200 8 pulse spectra were taken at 273 K, each consisting of 4 K points. The concentration of aldehyde was varied between 9.8 mmol ml^{-1} and 78.4 mmol ml^{-1}. The excess of Zn(*i*Pr)$_2$ was varied between 1 and 3 equivalents.

Signals of starting aldehyde were integrated against signals of diethyl ether (trace component of R_2Zn samples) or against remaining proton signals of the aromatic region of C_7D_8.

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References

1 K. Soai, T. Shibata, H. Morioka and K. Choji, *Nature (London)*, 1995, **378**, 767–768.
2 K. Soai, T. Shibata and Y. Kowata, *Japan Patent JP*, 9–268179, 1997.
3 T. Shibata, J. Yamamoto, N. Matsumoto, S. Yonekubo, S. Osanai and K. Soai, *J. Am. Chem. Soc.*, 1998, **120**, 12157–12158.
4 I. Sato, A. Ohno, Y. Aoyama, T. Kasahara and K. Soai, *Org. Biomol. Chem.*, 2003, **1**, 244–246; I. Sato, S. Osanai, K. Kadowaki, T. Sugiyama, T. Shibata and K. Soai, *Chem. Lett.*, 2002, 168–169;

I. Sato, K. Kadowaki, H. Urabe, J. H. Jung, Y. Ono, S. Shinkai and K. Soai, *Tetrahedron Lett.*, 2003, **44**, 721–724; I. Sato, Y. Matsueda, K. Kadowaki, S. Yonekubo, T. Shibata and K. Soai, *Helv. Chim. Acta*, 2002, **85**, 3383–3387; S. Tanji, A. Ohno, I. Sato and K. Soai, *Org. Lett.*, 2001, **3**, 287–289; I. Sato, K. Kadowaki, Y. Ohgo, K. Soai and H. Ogino, *Chem. Commun.*, 2001, 1022–1023; I. Sato, R. Yamashima, K. Kadowaki, J. Yamamoto, T. Shibata and K. Soai, *Angew. Chem., Int. Ed.*, 2001, **40**, 1096–1099; I. Sato, K. Kadowaki and K. Soai, *Angew. Chem., Int. Ed.*, 2000, **39**, 1510–1514.

5 (*a*) K. Soai, T. Shibata and I. Sato, *Acc. Chem. Res.*, 2000, **33**, 382–390; K. Soai and I. Sato, *Chirality*, 2002, **14**, 548–554; (*b*) K. Soai and I. Sato, *Viva Origino*, 2002, **30**, 186–198; (*c*) In addition, see: D. K. Kondepudi and K. Asakura, *Acc. Chem. Res.*, 2001, **34**, 946–954; (*d*) M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez and J. C. Palacios, *Chem. Commun.*, 2000, 887–892; (*e*) B. L. Feringa and R. A. vanDelden, *Angew. Chem., Int. Ed.*, 1999, **38**, 3419–3438.

6 F. C. Franks, *Biochim. Biophys. Acta*, 1953, **11**, 459–463.

7 M. Calvin, *Chemical Evolution*, Oxford University Press, Oxford, 1969, ch 7.

8 P. Decker, *Origins Life*, 1975, **6**, 211–218; P. D. Bailey, *Chem. Commun.*, 1995, 1798–1799.

9 (*a*) D. G. Blackmond, C. R. McMillan, S. Ramdeehul, A. Schorm and J. M. Brown, *J. Am. Chem. Soc.*, 2001, **123**, 10103–10104; (*b*) An essentially similar conclusion concerning the involvement of a homochiral dimer catalyst was subsequently reached in the analysis of autocatalytic reactions carried out at −25 °C: I. Sato, D. Omiya, H. Igarashi, K. Kato, Y. Ogi, K. Tsukiyama and K. Soai, *Tetrahedron: Asymmetry*, 2003, **14**, 975–979.

10 C. Girard and H. B. Kagan, *Angew. Chem., Int. Ed.*, 1998, **37**, 2923–2959.

11 V. I. Goldanskii and V. V. Kuz'min, *Z. Phys. Chem. (Leipzig)*, 1988, **269**, 216–274; see: D. G. Blackmond, *Adv. Synth. Catal.*, 2002, **344**, 156–158.

12 D. A. Singleton and L. K. Vo, *J. Am. Chem. Soc.*, 2002, **124**, 10010–10011.

13 K. Soai, I. Sato, T. Shibata, S. Komiya, M. Hayashi, Y. Matsueda, H. Imamura, T. Hayase, H. Morioka, H. Tabira, J. Yamamoto and Y. Kowata, *Tetrahedron: Asymmetry*, 2003, **14**, 185–188.

14 I. Sato, H. Urabe, S. Ishiguro, T. Shibata and K. Soai, *Angew. Chem., Int. Ed.*, 2003, **42**, 315–318.

15 The detailed solution structure of the Zn alkoxide product will be discussed in ensuing publications. For the moment, a racemic sample gives two superposable 1-H NMR spectra corresponding on the one hand to *R,S*-alkoxide and on the other to *R,R*- or *S,S*-alkoxide, exchange being slow on the NMR timescale at ambient temperature. The two may be readily distinguished in the aromatic region around 8.6 ppm, with the racemate at lower field.

16 Professor D. G. Blackmond has carried out an extensive study of the precipitation phenomenon under catalytic turnover conditions; private communication.

17 See ref. 13; in the present case the three Et_2O results reported in Fig. 3 are 37*(R)*, 20*(R)* and 90(*S*) ee.

18 K. Mislow, *Collect. Czech. Chem. Commun.*, 2003, **68**, 849–864.

19 This derivation is normally attributed to W. H. Mills, *Chem. Ind.*, 1932, 750, but has a longer history described in Mislow's review (ref. 16). For an interesting discussion see S. F. Mason, *Chemical Evolution*, Clarendon Press (OUP), Oxford, 1992, pp. 266 ff. For a recent formal derivation see: K. Iwamoto, *Phys. Chem. Chem. Phys.*, 2002, **4**, 3975–3979 and papers by the author cited therein.

20 This differs from the interpretation offered in our original paper (ref. 9), but caution is warranted by the fact that DFT calculations indicate that the macrocyclic dimer postulated there is not the lowest energy structure by a significant margin.

21 Representing an ideal, since the real system will involve continual spontaneous reactions that will diminish in significance as the autocatalytic process gradually becomes dominant. The idea that the statistical enantiomeric excess in a stochastic mechanism is dependent on the initial pool provided by the background reaction is implicit in the discussions in ref. 9*b* and ref. 11.

22 F. G. Buono and D. G. Blackmond, *J. Am. Chem. Soc.*, 2003, **125**, 8978–8979.

23 For general reviews of Zn alkylations see: L. Pu and H. B. Yu, *Chem. Rev.*, 2001, **101**, 757–824; K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833–856.

24 M. Quack, *Angew. Chem., Int. Ed.*, 2002, **41**, 4618–4630; P. Cintas, *Angew. Chem., Int. Ed.*, 2002, **41**, 1139–1145; G. Zubay and A. Schechter, *Chemtracts*, 2001, **14**, 291–296; P. Frank, W. A. Bonner and R. N. Zare, *Chem. 21st Century*, 2001, 175–208; M. Bolli, R. Micura and A. Eschenmoser, *Chem. & Biol.*, 1997, **4**, 309–320; W. A. Bonner, *Top. Stereochem.*, 1988, **18**, 1–96.

25 J. K. Laerdahl, P. Schwerdtfeger and H. M. Quiney, *Phys. Rev. Lett.*, 2000, **84**, 3811–3814.

26 I. Weissbuch, L. Leiserowitz and M. Lahav, *ACS Symp. Ser.*, 2002, **810**, 242–253; I. Weissbuch, I. Kuzmenko, M. Berfeld, L. Leiserowitz and M. Lahav, *J. Phys. Org. Chem.*, 2000, **13**, 426–434; W. A. Bonner, *Origins Life Evol. Biosphere*, 1996, **26**, 27–46; W. A. Bonner, *Origins Life Evol. Biosphere*, 1994, **24**, 63–78; Y. Takanishi, H. Takezoe, Y. Suzuki, I. Kobayashi, T. Yajima, M. Terada and K. Mikami, *Angew. Chem., Int. Ed.*, 1999, **38**, 2354–2356; A. Collet, M. J. Brienne and J. Jacques, *Chem. Rev.*, 1980, **80**, 215–230.

27 A. M. Kierzek, *Bioinformatics*, 2002, **18**, 470–481 and refs therein.

28 P. Knochel, personal communication.

29 T. Shibata, S. Yonekubo and K. Soai, *Angew. Chem., Int. Ed*, 1999, **38**, 659–662.

30 T. Rho and Y. F. Abuh, *Synth. Commun.*, 1994, **24**, 253–256.