CRYSTAL GROWTH & DESIGN

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Controlling the Effect of Chiral Impurities on Viedma Ripening

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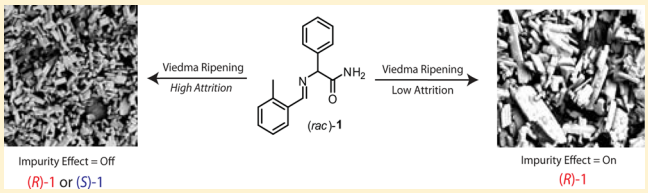
ABSTRACT: Spontaneous symmetry breaking and chiral amplification by means of Viedma ripening by definition should result in complete deracemization of a racemic conglomerate into either one of the enantiomers with equal probability. In practice, however, chiral impurities influence Viedma ripening and one enantiomer is obtained in preference over the other. Here, we show that by increasing the attrition intensity during Viedma ripening, the effect of chiral impurities is suppressed and deracemization does yield either enantiomer with equal probability. The reason for this is that the resulting smaller crystals lead to such a low surface density of chiral impurities that they no longer inhibit the crystal growth sufficiently to determine the chiral outcome. Furthermore, we show that even for low attrition intensities, the effect of chiral impurities can be canceled by using the right amount (10 ppm) of chiral additives.



INTRODUCTION

Chirality is a topic of paramount importance owing to the fact that both enantiomers of a compound can interact differently with various biomolecules (e.g., DNA, proteins, hormones) in the human body. As a result, pharmaceutical drugs must often be registered and, hence, produced in enantiopure form. Separation of enantiomers by chiral resolution is widely applied and a variety of methods are available (e.g., diastereomeric salts).[1] However, the maximum yield of chiral resolution is by definition limited to 50%. This limitation can be overcome if the compound can change its handedness in solution. An example of such a process is through spontaneous symmetry breaking, which was first discovered by Havinga who obtained enantiopure crystals from a supersaturated solution in which the compound is racemized.[2] This method was further developed by Kondepudi et al. who obtained enantiopure crystals through secondary nucleation by applying stirring-induced crystallization from a supersaturated solution. In this case, the material was achiral, thus no racemization was necessary.[3] Soai showed that spontaneous symmetry breaking followed by a chiral amplification mechanism in chemical synthesis results in enantiopure compounds through an autocatalytic reaction.[4,22]

Although the previous examples illustrate methods in which chiral purity can be achieved from solution, remarkably, even an initially racemic solid state can be deracemized into an enantiopure end state by means of attrition. This was discovered by Viedma for $NaClO_3$, a compound that is achiral in solution.[5] Noorduin et al. discovered that attrition-enhanced deracemization can also be applied to deracemize pharmaceutically relevant chiral molecules.[6] This process of deracemization is now called Viedma ripening, and its mechanism is based on conglomerate crystals which are in contact with a saturated solution.[7,8] Larger crystals grow, whereas smaller crystals dissolve due to the Gibbs−Thomson effect. Solute molecules of both enantiomers undergo racemization and can attach to larger crystals of either chirality. As a result of continuous attrition, chiral clusters are generated, and these chiral clusters merge enantioselectively with the larger crystals leading eventually to an enantiopure end state. The attrition causes the crystals to remain small, thereby speeding up the process.

Prior to chiral amplification, the initial symmetry of the system has to break. A number of different experimental approaches have been developed to break the initial symmetry of the system to ultimately give an enantiopure end state with a controlled handedness.[9,10] For instance, a controlled enantiopure end state can be obtained by starting with an initial enantiomeric excess (*ee*).[6] An initial difference in crystal size distribution (CSD) between the enantiomers can also direct the final chiral end state toward the initially larger crystals, even when the initial *ee* of the smaller crystals is higher.[11,12] Noorduin et al. showed that the chiral outcome can further be controlled using circularly polarized light.[13] Additionally, chiral additives can be used to control the final chiral end state, even in minute amounts.[6,14]

In the absence of any of these symmetry breaking agents, it is assumed that there is no enantiomeric preference for an end state of specific chirality due to the identical thermodynamic

Received: June 21, 2013
Revised: September 2, 2013

   dx.doi.org/10.1021/cg400927m | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

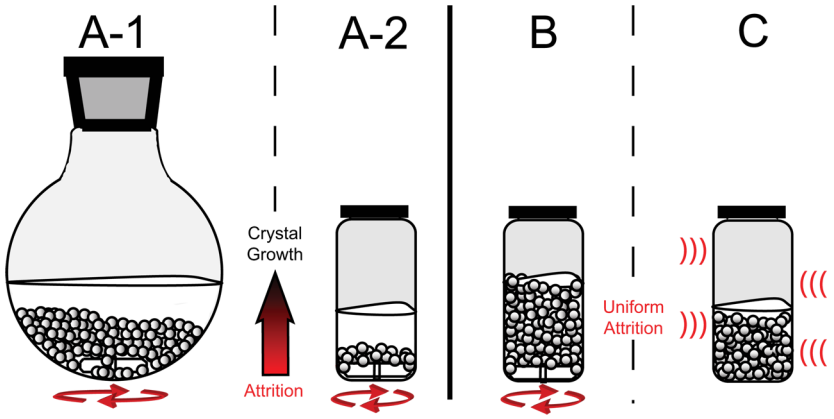


Figure 1. Schematic representation of the experimental configurations which have been used in the Viedma ripening experiments. Methods A-1 and A-2 represent systems in which the crystals are ground mainly in the lower part of the solution. Method B represents a system in which extra beads have been added, and method C represents a system in which ultrasonic waves were used instead of stirring.

properties of enantiomers. Therefore, spontaneous symmetry breaking from an exact racemic state should result in an end state of which the chirality should be either left- or right-handed dependent on random fluctuations. In practice, however, a stochastic chiral outcome as a result of spontaneous symmetry breaking has not been observed.

In a number of chiral crystallization experiments described in literature, including the reported Viedma ripening experiments, preferential symmetry breaking was observed, and often this preference was associated with the likely presence of "cryptochiral environmental effects".[2,15−20,24] It is indeed known that minute amounts of impurities well below the parts per million range can influence crystal growth.[21] However, to establish which kind of impurity is accountable for the initial symmetry breaking is challenging, if not impossible. There are literature reports in which the nonstochastic nature in symmetry-breaking experiments was investigated. Singleton and Vo proved experimentally that the initial preferential symmetry breaking in the Soai reaction was due to solvent choice and therefore possibly due to undetected chiral impurities, which could be present in the solvent.[22,23] Viedma also suggested that chiral impurities could control the chiral outcome in his experiments on $NaClO_3$.[24] More recently however, Hein et al. showed that by applying ultrasonic waves to deracemize an amino acid derivative by Viedma ripening, the chiral outcome was obtained in a stochastic fashion.[12] This is surprising because Viedma ripening using stirring-induced attrition of this compound resulted in preferential deracemization.[19] An explanation for these contrasting results is lacking.

It is of interest to neutralize the effect of chiral impurities since these impurities control the chiral outcome of Viedma ripening undesirably, even at very low concentrations. From model studies, it is known that at higher attrition intensities, the chiral outcome should be more stochastic.[25]

In this report, we show that Viedma ripening using higher attrition intensities indeed leads to an enantiopure end state in a stochastic fashion. Furthermore, by adding the right amount (10 ppm) of chiral additives which neutralize the effect of chiral impurities, we can obtain a stochastic outcome even when using mild attrition intensities.

■ EXPERIMENTAL SECTION

Each experiment was conducted using new equipment in order to avoid any (chiral) contamination. The batch of *N*-(2-methylbenzylidine) phenylglycine amide (**1**) used in the present experiments was also used in earlier experiments in which the chiral outcome always turned out to be (*R*)-**1**.[10] The *ee* of the racemic starting material was checked to be 0% within the detection limit of the chiral HPLC. Scintillation flasks and PTFE-coated octahedral magnetic stirring bars (length 25 mm, ø 10 mm) and PTFE-coated oval magnetic stirring bars (length 20 mm, ø 10 mm) were purchased from VWR. Glass beads (ø = 1.5−2.5 mm), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), phenylglycine (**2**, both enantiomers), and acetonitrile (ACN) were purchased from Sigma-Aldrich. The temperature was kept at 20 ± 2 °C for all experiments.

Deracemization Experiments. Viedma ripening experiments were conducted in four different setups (Figure 1).

Method A-1. A 100 mL round-bottom flask equipped with an octahedral magnetic stirring bar was charged with 4.0 g of (*rac*)-**1**, 20 g of glass beads, and 35 g of ACN. The suspension was ground for 1 h at 1300 rpm, after which 1.47 mL of DBU was added.

Method A-2. Method A-2 was conducted in a 20 mL scintillation flask with an oval magnetic stirring bar, using exactly ten times less material than in method A-1: 0.4 g of (*rac*)-**1**, 2.0 g of glass beads, 0.147 mL of DBU, and 3.5 g of ACN.

Method B. Method B was conducted in a 20 mL scintillation flask with an oval magnetic stirring bar, using exactly ten times less (*rac*)-**1** and DBU than in method A-1: 0.4 g of (*rac*)-**1**, 0.147 mL of DBU but with 8.0 g of glass beads.

Method C. Method C was conducted in a thermostatted Fisher Bioblock Transsonic TI-H-10 ultrasonic bath using a frequency of 45 kHz and using the same amount of material as in method A-2: 0.4 g of (*rac*)-**1**, but with 5.0 g of glass beads and without a stirring bar. The suspension was sonicated for 15 min, after which 0.147 mL of DBU was added.

Sampling. About 0.2 mL of slurry was taken from the suspension by means of a pasteur pipet and was subsequently subjected to vacuum filtration on a P4 glass filter (ø 10 mm). The residual crystals were washed on the filter using 0.5 mL of methanol in order to remove DBU and the mother liquor. The crystals were then dissolved in 1.5 mL of 2-propanol and the *ee* was determined by means of chiral HPLC.

Chiral HPLC Analysis to Determine the *ee*. A Chiralpak AD-H (250 × 4.6 mm ID) column was used in combination with the following conditions: eluent *n*-heptane/2-propanol (95/5 v/v %), flow 1 mL/min, r.t., λ = 254 nm, 20 μL injection volume. Retention times: (*R*)-**1**, 30.1 min and (*S*)-**1**, 34.5 min.

Scanning Electron Microscopic Analysis to Determine the Crystal Size Distribution. After attrition of the crystals for 1 h (15 min for the ultrasound experiments) in the absence of DBU, a drop of the slurry was taken from the suspension during attrition and was immediately put on a sample holder. The solvent was removed using a flow of nitrogen within 1 s to avoid significant crystal growth. The

dx.doi.org/10.1021/cg400927m | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

sample was covered with a thin film of Pd/Au. The sample was subsequently analyzed using an FEI Phenom scanning electron microscope (SEM) in the back scattering mode. This procedure was repeated several times for each method to ensure reproducibility.

RESULTS AND DISCUSSION

Compound **1**, an amino acid derivative which crystallizes as a conglomerate in space group $P2_12_12_1$ and readily racemizes in solution using DBU as a catalyst, can be obtained in enantiopure form by means of Viedma ripening (Figure 2).[6]

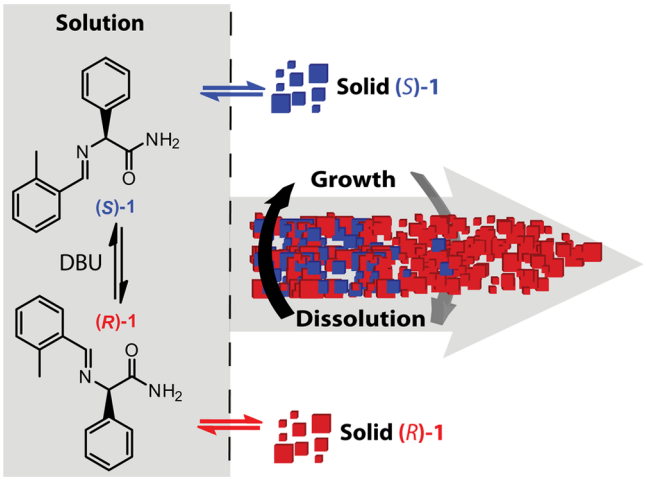


Figure 2. Viedma ripening of *N*-(2-methylbenzylidine)phenylglycine amide (**1**): racemization in solution (gray background) combined with crystal growth, ultimately results in an enantiopure crystalline end state in which the time to complete deracemization can be reduced considerably by attrition.

As previously reported, in the absence of symmetry-breaking agents, compound **1** was successfully deracemized more than 100 times.[10] The final chiral outcome from these experiments always turned out to be enantiopure (*R*)-**1**, thus with a 100% preference for the (*R*)-enantiomer. Preferential symmetry breaking was also observed in Havinga–Kondepudi resolution experiments with compound **1**.[18] These preferential symmetry-breaking results can be attributed to the likely presence of impurities. Although the nature of these impurities is unknown, for simplicity we refer to these impurities as being (*S*)-impurities.

Viedma ripening experiments have typically been conducted in round-bottom flasks (method A-1, Figure 1). To test if an increase in attrition intensity would suppress the effect of chiral impurities, Viedma ripening experiments were tested in scintillation flasks using exactly ten times less material (method A-2, Figure 1) as compared to method A-1. We expected that the attrition intensity in scintillation flasks would be higher because the crystals are closer to the stirrer bar as compared to attrition in round-bottom flasks. However, while complete deracemization was always achieved using method A-2, the final configuration was still always enantiopure (*R*)-**1**. To investigate if a further increase in attrition intensity would suppress the effect of chiral impurities, extra glass beads were added to method A-2. Indeed, Viedma ripening using this method (method B, Figure 1) did lead to complete deracemization in which the enantiopure end state was either (*S*)-**1** or (*R*)-**1** in a stochastic fashion (Figure 3).

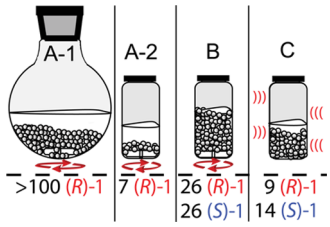


Figure 3. Results of Viedma ripening experiments using different methods. Each experiment resulted in complete deracemization to give enantiopure **1**.

Apparently, at higher attrition intensities, the effect of the (*S*)-impurity can be overruled. However, even at high attrition intensities, the (*S*)-impurity still affects the course of deracemization, as can be seen from Figure 4. Deracemization

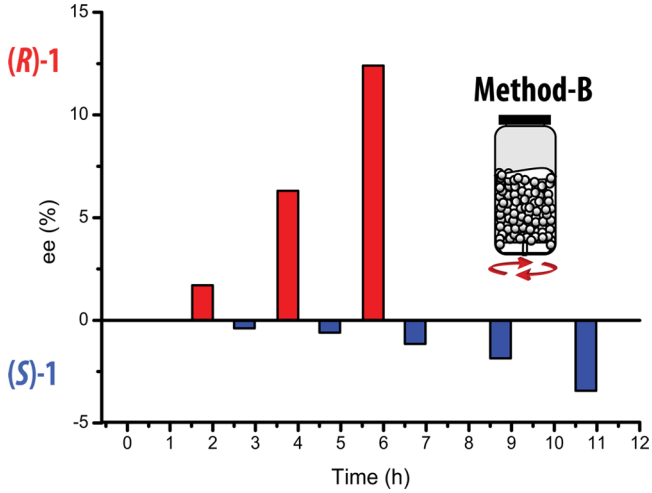


Figure 4. Comparison of the course of chiral amplification toward (*R*)-**1** (red) and toward (*S*)-**1** (blue) using method B.

toward (*R*)-**1** clearly proceeds faster than deracemization toward (*S*)-**1**. The (*S*)-impurity hampers the deracemization toward (*S*)-**1**, but the hindrance is not strong enough to control the end state of Viedma ripening.

Another way to achieve enhanced attrition is by applying ultrasound-assisted attrition (method C, Figure 1). Again, deracemization with ultrasounds no longer proceed preferentially toward the (*R*)-**1** end state (method C, Figure 3). This is consistent with the results of Hein et al. on a similar amino acid derivative.[12] Our results show that an increase in attrition intensity creates a stochastic chiral outcome. This could be explained by the resulting smaller crystal sizes of compound **1**. In order to get an indication of the overall crystal size during attrition for each method, samples of the slurry were taken and analyzed using scanning electron microscopy (SEM).

The SEM-images in Figure 5 clearly show that different crystal sizes are obtained, depending on which method is used. The needles are large (up to 100 μm) during attrition of compound **1** using methods A-1 or A-2. This is because in these methods, attrition of the crystals only occurs at the bottom of the solution (Figure 1). Due to a small vortex which is induced by stirring, crystals can transfer to the top of the solution where the attrition intensity is minimal. As a result, the crystals can grow significantly in size and remain, on average, large in size. Conversely, in method B, all the crystals are

dx.doi.org/10.1021/cg400927m | Cryst. Growth Des. XXXX, XXX, XXX–XXX

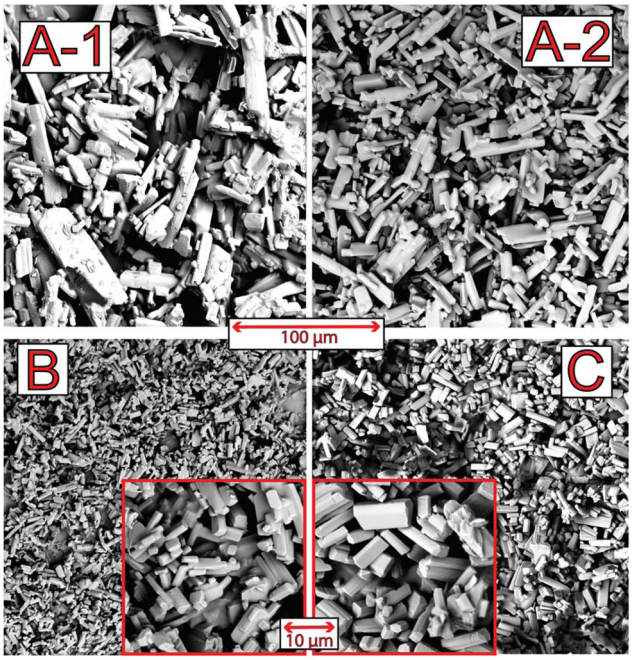


Figure 5. SEM images taken after the attrition for 1 h of compound **1** in the absence of DBU in methods A-1, A-2, and B and after 15 min in method C.

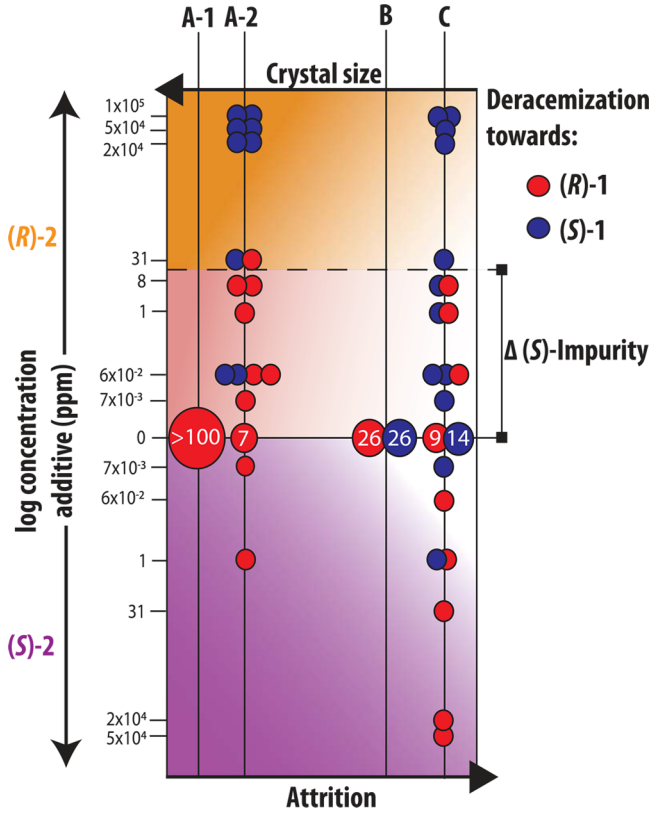


Figure 6. Schematic overview of the chiral outcome of Viedma ripening experiments of **1** in the presence and absence of phenylglycine (**2**) using results from previous[10] and current experiments. Concentration of **2** (log scale) is plotted against attrition intensity (see Experimental Section). The gradient of the background color represents the surface density of additives/impurities. Each sphere represents the chiral outcome of one Viedma ripening experiment, unless specified otherwise.

continuously ground and, therefore, the needle-shaped crystals remain small in size (up to 10 μm). Due to the uniform attrition created by ultrasound in method C, the crystals have a size comparable to method B. If the average crystal size of **1** is smaller, then the average crystal surface area of **1** is larger and, as a consequence, the surface density of impurities is smaller.

We have thus demonstrated that the effect of chiral impurities can be suppressed by enhanced attrition. Next, we aim to neutralize the effect of these impurities by intentionally adding additives of opposite chirality. This method of titration should not only work at high attrition intensities but also for moderate attrition intensities, as in methods A-1 and A-2. Therefore, we determined the effect of many additive concentrations of both handedness on the chiral end state of **1**, and these results are summarized in Figure 6.

Enantiopure phenylglycine (**2**) was used as a chiral additive, since it has been shown to be effective in controlling the deracemization of **1**.[6] As expected, at concentrations of additive **2** of 2×10^4 ppm and higher, the chiral end state of **1** was always opposite to that of the additive (i.e., it follows Lahav's rule of reversal).[6,26] This was observed for all experiments, independent of the attrition intensity. If the attrition intensity is moderate (method A-2), as little as 30 ppm of (*R*)-**2** was required to neutralize the effect of the unknown (*S*)-impurities. At lower concentrations of additive (*R*)-**2**, the effect of the (*S*)-impurities dominates at moderate attritions. However, we also observed that in two experiments at a concentration of 6×10^{-2} ppm of (*R*)-**2**, the additive determined the end state to become (*S*)-**1**. Lack of material prevented us from obtaining more stastistics on this. On the other hand, in the presence of 1 ppm or lower of additive (*S*)-**2**, the final chiral outcome was (*R*)-**1**, which was as expected due to the combined effect of the additive and the (*S*)-impurities at moderate attritions. As we have demonstrated earlier, in the absence of additives, only the (*S*)-impurities control the end state at moderate attrition intensities toward enantiopure (*R*)-**1**. However, if the attrition intensity is high (as in method-B and method-C), neither the additive nor the chiral impurities determine the end state at additive concentrations of 30 ppm and lower. This is because the enhanced attrition causes the surface density and thus the effect of the additives/impurities to become negligible (light shaded area, Figure 6). Additive concentrations of 2×10^4 ppm or higher still determine the chiral outcome, even at high attrition rates.

Throughout the initial stage of Viedma ripening and in the absence of symmetry-breaking agents, no significant *ee* exists and the overall crystal size distribution of the enantiomers is symmetric. Due to random fluctuations in time, the system will arrive at a point in which the *ee* or the difference in the crystal size distribution between the enantiomers is (locally) large enough to amplify the small difference and to set off the process of deracemization. Deracemization will then proceed to the enantiomer, which at that point happens to have an *ee* or a larger crystal size distribution.

However, if chiral impurities are present, the symmetry is broken from the beginning. Chiral impurities inhibit the growth of one of the enantiomers, whereas the other enantiomer is affected to a smaller extent and is allowed to grow larger in size. Consequently, the average crystal size of one of the enantiomers is larger than the other, and this in turn determines the process of deracemization toward the enantiomer which has the largest crystals.

dx.doi.org/10.1021/cg400927m | *Cryst. Growth Des.* XXXX, XXX, XXX−XXX

The consequence of a high attrition intensity is smaller crystals and thus a larger total surface area of compound **1**. As a result of the large surface area, the surface density of the chiral impurities becomes smaller. In our case, the surface area of compound **1** in methods B and C is roughly 10 times as large as the surface area in method A (Figure 5), and the surface density of the chiral impurities on the crystals is expected to be about 10 times smaller. We expect that the majority of the chiral impurities are adsorbed on the crystal surface of compound **1**. This is only true if the total number of surface sites of compound **1** significantly exceeds the total amount of impurity molecules in the system. We estimate this by assuming for methods B and C an average crystal size of 10 μm and a crystal needle aspect ratio of 10. We find that at a level of 10 ppm of impurity, roughly 10^4 places on the crystal surface of compound **1** are available for each impurity molecule. This very low coverage leaves room for overruling the effect of the additive/impurity in method C. Another consequence of a high attrition intensity is the reduced time for the impurities to stereoselectively inhibit the crystal growth. The crystals are allowed to grow only for a very short time before being fractured, and as a consequence, there is insufficient time for the impurities to inhibit the growth of one of the enantiomers significantly. In this case, the difference in crystal size between the enantiomers is insignificant and therefore the initial symmetry will break by chance, leading to a stochastic outcome.

Our results show that a small change in the Viedma ripening setup or conditions can drastically alter the course of Viedma ripening if impurities or additives are present. This is important to keep in mind when, for instance, a Viedma ripening process has to be scaled up to an industrial scale because impurities may suddenly determine the handedness of the final state.

The effect of chiral impurities during Viedma ripening experiments can be suppressed by applying high attrition intensities. As a result, the surface density of chiral impurities becomes smaller, and therefore, the chiral impurities cannot inhibit the crystal growth sufficiently. Additionally, at low attrition intensities, the effect of chiral impurities during Viedma ripening can be neutralized by adding the right amount of counter additive. Only minute amounts of additive (approximately 10 ppm) are required to break the initial symmetry and to give a controlled enantiopure end state.

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Notes

The authors declare no competing financial interest.

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