Asymmetric Amplification

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Generation of Highly Enantioenriched Crystalline Products in Reversible Asymmetric Reactions with Racemic or Achiral Catalysts[**]

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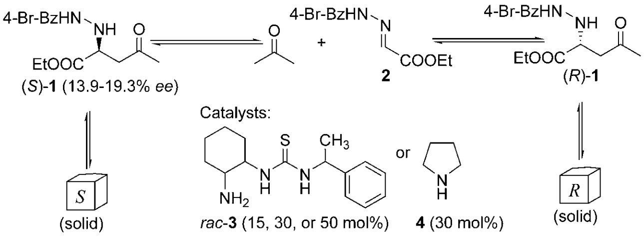
The generation of enantiomerically pure compounds from achiral precursors is the dream of any stereochemist. Except in enzymatic reactions, such a high degree of stereoselectivity is usually out of reach. Closely related is one of the greatest unsolved problems of our time in chemistry: the origin of homochirality in the biosphere; that is, the fact that L-amino acids and D-sugars dominate in nature, while laboratory experiments with stereoselective reactions under achiral conditions only produce a racemic mixture.[1–3] Many scientists assume that the choice of a single chirality occurred before the advent of life on early earth.[4,5] Offering a potential solution to this conundrum, in 1953 the crystallographer Charles Frank first introduced the concept of “spontaneous chiral symmetry breaking” in chemistry.[6] In such a process, one enantiomer is preferentially formed in a kinetically controlled autocatalytic process, even though the initial conditions were achiral. The first such symmetry-breaking transformation in chemistry was the homogenous Soai reaction. This reaction, however, is irreversible and thus couldn’t produce enantiomerically pure products.[7] Saito and Hyuga first realized that a reaction network must be reproductive to allow complete chiral symmetry breaking, resulting in 100% enantiomeric excess.[8]

Another rather different symmetry-breaking mechanism was reported by Kondepudi et al. for enantiomorphous crystallization from supersaturated $NaClO_3$ solutions on cooling under the influence of stirring, which causes secondary nucleation: one crystal handedness always randomly dominated in the solid product with 99% *ee*.[9] In 1999, Kondepudi et al. reported that even an intrinsically chiral, atropisomeric 1,1′-binaphtyl species is able to crystallize from the melt in high enantiomeric excess of 80% in a deterministic fashion (but with equal probability for the *R* and *S* crystal forms),[10] extending on earlier work of Pincock et al., who found a near Gaussian distribution of *ee* values centered around the racemic outcome.[11] This result was explained by secondary nucleation in conjunction with autocatalytic crystal growth; this process was later kinetically modeled by Asakura and co-workers.[12]

Viedma expanded on this work and obtained completely monochiral states from previously racemic crystal mixtures of $NaClO_3$. This result was explained by a combination of nonlinear autocatalysis and recycling through dissolution of crystallites spawned off from the mother crystals by grinding.[13–16] Very recently, Noorduin et al. demonstrated convincingly that practically racemic or scalemic conglomerates of another intrinsically chiral compound, an amino acid derivative, can fully deracemize by solution-phase enantiomerization in a base-catalyzed process.[17] Although such a process offers fascinating prospects for the production of enantiomerically pure compounds, not all chiral products of interest might enantiomerize readily, or they could be sensitive to the enantiomerization reaction conditions (e.g. giving side products stemming from rearrangements or elimination reactions). Moreover, products with more than one stereocenter might deracemize in an undesired way, because the synthesis of such complex chiral compounds demands that the chirality at each stereocenter be controlled individually.

Hence, understanding that the enantiomerization might also occur through the reactant (that is, involve the reverse reaction in a reversible stereoselective reaction),[18] we realized that the product of an enantioselective reaction run near equilibrium (under thermodynamic control) could readily deracemize under mild conditions, for example, in the presence of a suitable achiral or racemic catalyst or even without a catalyst at all. Herein we demonstrate such a deracemization process by example of a reversible Mannich type reaction (Scheme 1), and we explain the observed process by a kinetic rather than a thermodynamic model that involves recycling by denucleation and nonlinear autocatalytic crystal growth.

We recently observed an increase in product *ee* values when a slurry of a racemic mixture of the preformed



Scheme 1. Deracemization experiments with a Mannich type reaction carried out in toluene at room temperature with racemic or achiral catalysts. 4-Br-Bz = 4-bromobenzoyl.

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crystalline Mannich product **1**[19] was stirred in its saturated solution with a soluble enantiopure primary amine thiourea catalyst (**3**). We assumed that the enantiomerization of the product in solution could be involved and that it might occur via the prochiral reactant **2**. To test this hypothesis, and because we recently became aware of the remarkable observations of Noorduin et al.,[17] we set up a series of experiments in which we, in effect, made the asymmetric reaction that we studied earlier[19] run backwards: partly dissolved mixtures of the crystalline product conglomerates with varied but low initial *ee* values were vigorously stirred together with achiral catalyst **4** or racemic catalyst **3** (Scheme 1), which was added in different amounts (see Figures 1 and 2 and the Supporting Information). We carried out experiments both with and without glass beads and at constant stirring rates (1300 rpm). All the experiments show a clear trend of asymmetric amplification with progressing reaction time. All *ee* values given in Figures 1 and 2 refer to samples taken from the product slurry.

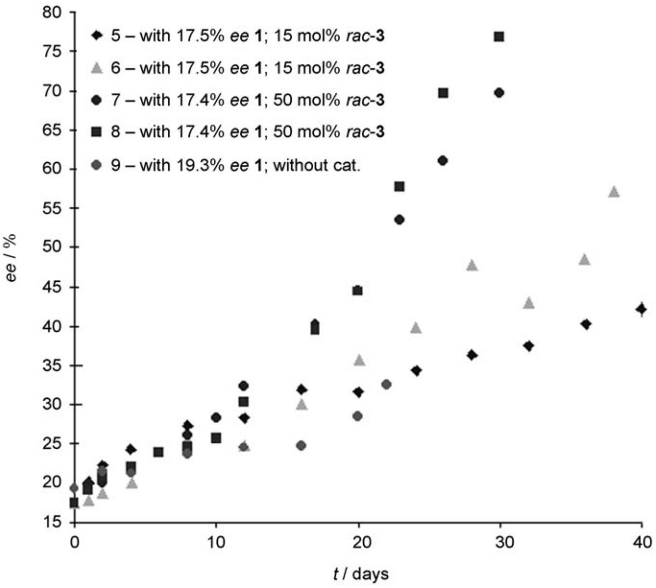

Figure 2. Enantiomeric excess value versus time determined from the slurry for the Mannich product **1** in the deracemization process shown in Scheme 1 (run 8 without glass beads; runs 5–7 and 9 with glass beads). Runs 5 and 7–9 were carried out with (*S*)-**1**; run 6 was performed with (*R*)-**1**.

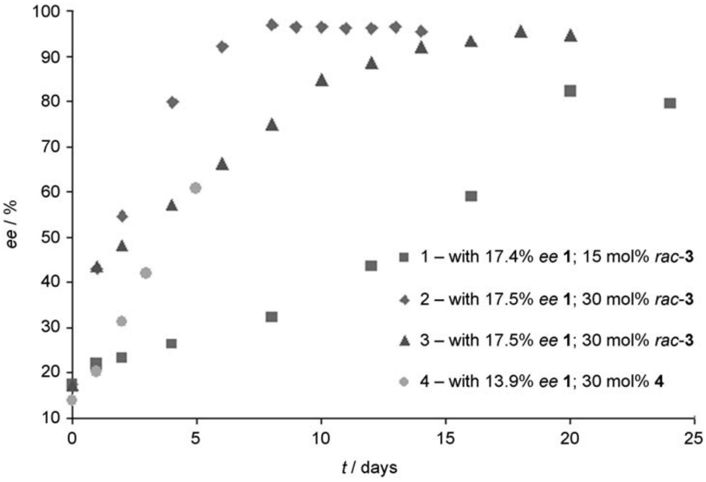

Figure 1. Enantiomeric excess values versus time determined from the slurry for the Mannich product **1** in the deracemization process shown in Scheme 1 (runs 1 and 3 without glass beads; runs 2 and 4 with glass beads).

We observed that the enantiomeric excess of the solution–solid mixture increased slowly but clearly when the initial enantioimbalance in the solid Mannich product **1** was already significant (17.4 % *ee*), for example to 79 % *ee* after 24 days in experiment 1 in the presence of 15 mol % of *rac*-**3** and without glass beads (Figure 1). An increase in catalyst loadings from 15 to 30 mol % (runs 2 and 3) resulted in faster asymmetric amplification and higher attainable *ee* values. After final workup (filtration of crystals and washing with toluene), the solid-phase *ee* values for these two runs (2 and 3) were determined to be 100 and 98.5 %, respectively. This finding demonstrated that even complete homochirality in the solid state can be achieved by this method. Enantiomeric excess values in the samples withdrawn from the slurry were about 5 % smaller (95.5 % *ee* (2) and 94.6 % *ee* (3), Figure 1) than those from the solid, indicating a considerably lower solution *ee*. Notably, we always observed a deterministic outcome in the experiments with significant initial product *ee* (13.9–19.3 %): starting product absolute configuration was conserved during the whole course of the reaction.

Experiment 5 (Figure 2) is essentially a repetition of run 1 (Figure 1), with nearly identical initial conditions (17.5 instead of 17.4 % initial *ee*), but glass beads were present in run 5. Accordingly, results differed between the two runs, which also implies a probable temperature influence, which was not controlled for during the experiments: for example, run 1 gave product with 79 % enantiomeric purity after 24 days, while run 5 had produced crystalline product with only 34.4 % *ee* (from slurry) after the same reaction time. We also compared the results with catalyst **3** and glass-bead-assisted attrition (i.e. with grinding, runs 2, 5, 6, and 7) with those runs without glass beads in which the product crystals were only stirred (1, 3, and 8). In some cases (e.g. cf. experiments 7 and 8 with 17.4 % initial product *ee* and 50 mol % catalyst loading), the asymmetric amplification was faster or more sustained without glass beads than for experiments in which glass beads were added to the stirred crystal conglomerate. After 30 days, run 8 gave chiral product in 76.8 % enantiomeric excess without glass beads, while 69.8 % *ee* was obtained in the concurrent run 7 with glass beads. Notably, the highest catalyst loadings (runs 7 and 8) do not lead to improvement over runs 2 and 3. In all experiments we observed formation of reactant **2** (confirmed by NMR spectroscopy and mass spectrometry), thus verifying the involvement of enantiomerization via the reverse reaction.

To better understand the role of the catalyst, we also carried out a control experiment without any catalyst (run 9, Figure 2). Interestingly, we nevertheless measured an increase in the *ee* value to 32.6 % after 22 days from an initial 19.3 %

ee. We explain this finding by the fact that the Mannich reaction is already reversible and does not necessarily need the further assistance of a catalyst. However, another control experiment with a starting *ee* value of 0.2 % (*S*) and without added catalyst gave only 0.5 % *ee* (*S*) after 32 days. It appears that significant asymmetric amplification in reasonable reaction times requires significant initial enantioimbalance.

Extended reaction times might even have adverse effects, because side reactions could become significant, in particular when the reaction runs for several weeks. The reverse of the reaction depicted in Scheme 1, for example, gives both the *E* and *Z* forms of hydrazone **2** (the *Z*/*E* isomerization is slow).[20] However, only the *E* isomer can react in the forward reaction step to give the Mannich product **1** with catalyst **3**.

To see the effect of a different, simpler, and cheaper catalyst, we also employed pyrrolidine (**4**). The deracemization process is remarkably fast with **4** in the presence of glass beads (an increase in Mannich product *ee* value from 13.9 to 60.6 % was observed after only five days, see run 4, Figure 1). While both *rac*-**3** and **4** catalyze the deracemization process by reversible formation of reactant **2**, pyrrolidine might additionally act as a base, abstracting a proton from the CH-acidic position in **1** (run 4, Figure 1), which would also result in deracemization, in analogy to the recently reported DBU-catalyzed bimolecular enantiomerization of an amino acid derivative (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene).[17,21] Thus, the chiral product **1** might also enantiomerize directly with pyrrolidine (i.e. without involvement of the reactant **2** in the process $S \rightarrow R$ or $R \rightarrow S$). To see whether pyrrolidine and/or DBU could catalyze the Mannich type reaction itself, we added them to separate reaction mixtures. Intriguingly, we found that pyrrolidine is able to catalyze the reaction of **2** with acetone, while DBU is not (no product formation was detected). Instead, 4-bromo-*N*-benzoylhydrazine was formed as a result of the fragmentation of reactant **2**.

Notably, some enantioselective reactions that give a chiral product with a CH-acidic position might even be more tractable in the direct enantiomerization process than in enantiomerization via the reactant—for example, when the back reaction step is very slow (i.e. when practically irreversible product formation is involved, as, for example, in some asymmetric epoxidations) or when the desired chiral product is formed under kinetic control.

We have also continuously monitored the enantiomeric excess values in the solution and the solid state and compared the latter with the results from samples taken directly from the slurry before washing with toluene. We found that seven days after the start of the experiment (with an initial *ee* value of 17.5 % and 30 mol % **3**), the solid-state *ee* (or crystal enantiomeric excess) value of 77.3 % was dramatically higher than the *ee* values in the sample from the slurry (25.7 %). This finding indicates that the actual deracemization is probably much faster than the data depicted in Figures 1 and 2 implies. To find out whether one enantiomer has actually been transformed into its antipode, we isolated and purified the crystalline phase only after complete enantiomeric purity was achieved in a parallel run, to determine the total yield in the transformed conglomerate. Taking into account the unavoidable loss of solid product owing to dissolution at the beginning of the experiment, yields of at least 70 % were achieved, which means that the transformation of *R*-**1** into *S*-**1** must indeed have occurred. We anticipate that the deracemization might even become quantitative with larger batches and in the absence of side reactions.

Meyerhoffer's double solubility rule for the solubilities of racemic conglomerates with respect to monochiral crystals (in analogy to vapor pressures in ideal gases),[22] which had only recently been controversially discussed for the case of racemizing conglomerates,[23] appears to hold well for our system: the solubility of the enantiopure Mannich product **1** is 1.9 $\mathrm{g\,L^{-1}}$, while it is 4.5 $\mathrm{g\,L^{-1}}$ for *rac*-**1**. The rule predicts that a racemic conglomerate, consisting of two different species, should have exactly twice the solubility of a single enantiomer.[22] The observed deviation from the rule could be attributed to the nonideality of the solution.[24]

The dependence of the enantiomeric excess on the reaction time in our system is similar to that reported recently for the stirred slurry of an organic conglomerate, which, however was achiral in the solution phase.[25] In a logarithmic plot, the exponential increase of the *ee* values is clearly apparent (see the Supporting Information, Figure S1). This result is in accord with the predictions from two recent models for the deracemization of racemic conglomerates involving solution-phase enantiomerization,[17b,26] a transformation first studied by Havinga in 1941.[27] He reasoned that because of the faster "deposition" of those molecules from the stagnant solution that already dominate in the crystal phase, the transformation from the less abundant to the more abundant form must be inevitable once the enantiomerization process is fast enough, thus keeping the solution in its racemic state and resupplying the enantiomer which is taken away faster from the solution.[27b] Havinga employed supersaturation as the driving force in the crystallization process. Recently, it was proposed that recycling by thermodynamically controlled dissolution in a vigorously stirred slurry together with kinetically controlled nonlinear autocatalytic nucleation and crystal growth could explain these phenomena in merely saturated (not supersaturated) solutions.[28] The crystal growth is autocatalytic, because the bulk crystal surface must be involved in it. Crystal growth of the major isomer must be faster than its dissolution; while the rate of dissolution is proportional to the mole fraction of the respective crystal enantiomorph, the crystallization rate should have a more than linear dependence on the available crystal surface (or the mole fraction) of that enantiomorph.

Stirring, especially in the presence of glass beads, causes "secondary nucleation" by spawning off tiny microcrystals or clusters[16,26,29] from the mother crystals through crushing or shear forces. The rate of this secondary nucleation for a specific crystal handedness is obviously proportional to the grinding rate and to the mole fraction of the respective enantiopure mother crystals.[30] The microcrystals have the same handedness as their mother crystals and usually differ in size among each other. The ensemble of crystals obtained from vigorous stirring or grinding is permanently at non-equilibrium. It is fuelled by the influx of mechanical energy, as the thermodynamic energy content of the microcrystals increases with decreasing size according to the Gibbs–

Thomson rule.[31] Smaller crystals have a higher interfacial energy, because their surface is more strongly curved. Furthermore, the surface tension also has a higher contribution to the total energy of such a microcrystal because of the larger surface-to-volume ratio with decreasing size. The solubility of the smaller microcrystals is therefore enhanced with respect to the larger ones. This denucleation process[32] provides a simple and straightforward way of recycling the crystalline product of the minor enantiomer, exposing it to potential enantiomerization and recrystallization with the dominant enantiomorph, thereby offering an explanation for the observed total conversion of one enantiomer into the other (run 2, Figure 1).

Based on the insight that the only thermodynamically stable final state should consist of a large monochiral single crystal with minimal surface energy, it has been proposed recently that "Ostwald ripening", in which larger crystals grow at the cost of smaller ones, could constitute a deterministic route towards a final state with single chirality in a thermodynamically driven process under laboratory conditions.[17,33] In this case, Ostwald ripening would play the role of supersaturation in providing the driving force for crystallization in the non-equilibrium system. However, the authors themselves noted[17b] that without further assumptions, their model does not correctly predict the outcome for compounds which are achiral in solution (i.e. with an infinite rate of enantiomerization), as, for example, in the original Viedma experiment.[13,17b]

To provide a plausible model of the required nonlinear growth, Uwaha proposed, on the basis of earlier expectations,[12,14,29,34] that crystal growth is partly nurtured from coalescence of chiral clusters with the corresponding bulk crystals, resulting in a nonlinear autocatalytic feedback loop with a kinetic instability of the racemic state and a bifurcation in the crystal *ee* values, while the solution becomes and remains exactly racemic for sufficiently high enantiomerization rates.[26] A central feature of the Uwaha model is the temporary excess in the minor-enantiomer concentration in solution during the symmetry-breaking transition when enantiomerization in the solution is slow.[35] Experimentally, we have indeed found that vigorously grinding a slurry of scalemic conglomerate of *S*-**1** with 17.5 % initial solid–state *ee* for 19 h without catalyst resulted in a crystal *ee* increase to 33.7 % (after washing with toluene), while the solution-phase *ee* value is a mere 0.6 % *R*. After 60 h, the solid-state *ee* value was essentially unchanged (32.5 % *ee*). This experiment was repeated several times and with different initial solid-state *ee* values. In all cases, we observed rapid asymmetric depletion in the solution, which is usually accompanied by a tiny but significant excess of the solid phase's minor enantiomer.

In a subsequent deracemization experiment in the presence of catalyst **3**, we again observed that the solution phase remained nearly racemic most of the time, with an intermittent sudden increase in the minor form's enantiomeric excess up to 21 % *ee* (*R*), which might be due to a very slow enantiomerization process.[26,27] Indeed, the observed rate of racemization in the homogenous solution is surprisingly low and is found to be only slightly increased by the presence of the catalyst **3**. The half-life of nearly enantiopure **1** (at 99 % *ee*) is about 20 days in a homogenous near-saturated solution in the presence of three equivalents *rac*-**3**, which is a realistic concentration of the readily soluble catalyst in the deracemization experiments (Figures 1 and 2). It appears, therefore, that solution-phase enantiomerization cannot be made responsible for the observed swift asymmetric depletion in the solution under the influence of grinding or vigorous stirring in our heterogeneous system. Hence, while the stagnant solution should have approximately the same composition as the conglomerate, we assume faster removal of the crystal phase's major enantiomer from the solution owing to nonlinear crystal growth driven by the non-equilibrium distribution of crystal sizes.

The observed low racemization rate also made us wonder whether a polymorphic transition (e.g. induced by grinding) from a metastable racemic phase to a potentially more stable enantiomerically pure phase could be involved in our deracemization experiments.[36] However, in light of the solid evidence for the involvement of **3** both in the forward reaction[19] and in the whole transformation process (Figures 1 and 2 and the Supporting Information), and because of the absence of evidence for the existence of a metastable racemic phase in the solubility data, we consider a kinetically controlled crystal growth process in combination with an assisted enantiomerization involving the solution phase in the heterogeneous system to be the most probable explanation for our results. Furthermore, the observed first-order kinetics of the asymmetric amplification appear to fit better into a kinetic than a thermodynamic model. To reconcile the observation of a very low enantiomerization rate in the homogenous solution with the swiftness of the transformation process under heterogeneous conditions, we assume that the enantiomerization occurs much more rapidly at or near the crystal–solution interface,[37] in contrast to the results reported recently.[17]

In conclusion, the combination of stirring (with or without grinding) of preformed crystalline conglomerates of chiral products (with initially low enantiomeric excess values) of asymmetric reactions (e.g. the reversible Mannich type reaction studied herein) with enantiomerization through the reverse reaction might be a very promising new methodology to attain highly enantioenriched products (up to 100 % *ee*). For the first time it was shown that glass-bead-assisted attrition is not a necessary ingredient. The enantiomerization through the back reaction of a reversible asymmetric reaction could be a complement to the process revealed by Noorduin et al.,[17] thus extending the scope of exploitable chemical processes from direct enantiomerizations to reversible asymmetric reactions. Application of this concept to asymmetric transformations that provide only poor product enantiomeric excess values or conversion rates because of their reversibility might prove fruitful by converting such processes into valuable methods to give highly enantioenriched products.[38] Further mechanistic investigations are necessary to elucidate the exact nature of the transformation process reported herein. The challenge remains to accelerate the transformation process to make it more suitable as a method of deracemization for broad practical use.

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[38] The method described herein might be compared with the recently demonstrated symmetry breaking in homogenous reversible reactive systems closed to matter flow, see: M. Mauksch, S. B. Tsogoeva, S.-W. Wei, I. M. Martynova, *Chirality* **2007**, *19*, 816.