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Enantioenrichment by Iterative Retro-Aldol/Aldol Reaction Catalyzed by an Achiral or Racemic Base

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Direct resolution of racemic or scalemic conglomerates by crystallization has recently emerged as an alternative to the separation of enantiomers by means of an additional chiral compound such as the crystallization as diastereomeric salt or inhibition of one of the enantiomorph's crystallisation by addition of tailor-made additives.[1,2] In contrast to the latter techniques, the combination of resolution by crystallization and racemization in solution allows to obtain the enantiopure compound in up to quantitative yield.

By means of abrasive grinding Viedma achieved a complete resolution of intrinsically achiral $NaClO_3$ starting from a racemic mixture of the two enantiomorphic solid.[3] In this context, the term "chiral amnesia" was introduced in order to describe the loss of the solid-phase chiral identity (as L or D crystal) during dissolution.[4] The resulting racemization and the continuous preferential crystallization of the enantiomer that already dominates the solid phase was suggested to be the driving force for establishing homochirality in the solid phase as it enables the transformation of one solid enantiomer into the other via the solution phase.[4,5]

Several models have been developed to explain the deracemization process under grinding. Kondepundi proposed that in supersaturated solutions or melts secondary nucleation in conjunction with autocatalytic crystal growth is the driving force for the amplification process.[6] Ribó stated that the autocatalytic crystal growth is driven by chiral interactions between chiral aggregates in solution and the solid phase.[7] These interactions, which also direct the aggregation of two or more molecules, are favorable between homochiral partners and destructive between partners of different chirality. In this scenario the system is striving for the thermodynamically most stable state, which is homochirality. Also in the absence of supersaturation the trend towards homochirality is thermodynamically controlled and caused by two interplaying processes: continuous attrition of crystals by the grinding and Ostwald ripening.[5,8,9] The latter states that large crystals grow at the cost of smaller ones. Driving force for this process is the higher solubility of small crystals compared to larger ones due to their higher surface to volume ratio (Gibbs–Thompson effect).[10] Continuous grinding of the solid resupplies the number of thermodynamically less stable small crystals and amplifies thus the Ostwald ripening effect. A drawback of this theory is, however, that it cannot explain the exponential amplification of the initial enantiomeric excess that has been observed in Viedma's experiment.[3,11] Uwaha and Saito proposed microscopic models that describe non-linear kinetics for the autocatalytic chiral crystal growth.[11,12] Both models are based on the assumption that subcritical chiral clusters are formed by the grinding that can only be integrated into crystals of the same chirality. In Saito's model the transformation of one enantiomer into the other occurs directly on the crystal surface and is thus an autocatalytic process as well.

Recently, Noorduin et al. demonstrated that also nearly racemic or scalemic mixtures of intrinsically chiral compounds can quantitatively be resolved by means of the aforementioned grinding–racemization technique.[13,14] Since in this case the molecules do not lose their chiral identity upon dissolution, base-catalyzed racemization in solution via an achiral intermediate was the key to success. The protocol was shown to be effective even for epitaxial racemic conglomerates.[15] Using the example of naproxen it was shown that the deracemization time could significantly be reduced when the enantiomeric excess of the solid was kept high by a gradual in situ feed of racemic material.[16]

In a third type of deracemization, the forward- and back-reaction steps of a reversible organic reaction are key for the solution-phase racemization.[17] By using pyrrolidine as catalyst, Tsogoeva and co-workers generated reaction conditions that allowed to transform one enantiomeric Mannich product into the other via the reactants. Also in this system both abrasive grinding and the physical processes of aggregation and crystal growth provide the driving force for complete deracemization of the solid phase. From the observa-

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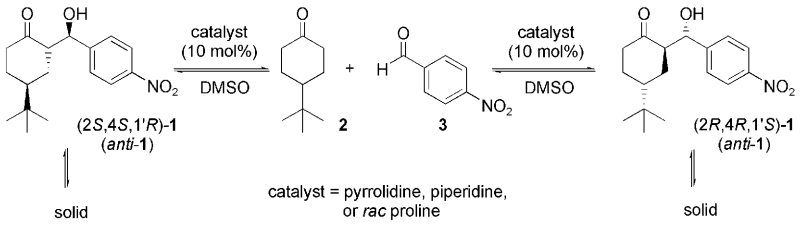
tion that the deracemization was faster than the racemization in solution, Saito's prediction[12] that the former process took place at the crystal/solution interface was verified experimentally.

Inspired by Tsogoeva's results and following our previous studies on the aldol reaction under grinding conditions, we report here an enantioenrichment of a scalemic aldol product via iterative retro-aldol/aldol reactions in presence of an achiral or racemic catalyst (Scheme 1).[18]



Scheme 1. Catalytic enantioenrichment of aldol product *anti*-**1** in presence of achiral or racemic secondary amines.

For the proof-of-concept experiment aldol product *anti*-**1**, which is known to form a conglomerate in the solid phase, was selected as starting material. In solution it can racemize in the presence of a catalytic secondary amine via the reactants 4-*tert*-butylcyclohexanone (**2**) and 4-nitrobenzaldehyde (**3**). Accordingly, solid-solution mixtures of scalemic *anti*-**1** were magnetically stirred (800 rpm) in DMSO in the presence of ZrO_2 beads as grinding medium. After 30 min, pyrrolidine (10 mol%) was added to provide racemization conditions in solution. Samples of the slurry were taken out over time, and the enantiomeric ratio (e.r.) of *anti*-**1** was determined by CSP-HPLC.

As we had hypothesized, the e.r. of *anti*-**1** in the slurry changed significantly over time (Figure 1). Starting from an initial 85:15 ratio it increased to 96:4 after one day, followed by 97.5:2.5 and 98:2 after two and eleven days, respectively. The enantioenrichment appeared to be fast in the beginning and then slowed down substantially. When the initial e.r. of the aldol product was 80:20, it raised to 95:5 after only two days and to 97:3 after seven days. In Figure 1 these data are presented as *ee* versus time.

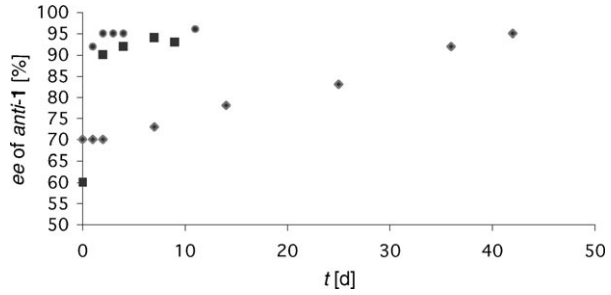


Figure 1. Enantiomeric excess of *anti*-**1** versus reaction time in the enantioenrichment shown in Scheme 1. Catalyst/starting *ee* of *anti*-**1** (for details see text): pyrrolidine 70% (●); pyrrolidine 60% (■); *rac*-proline 70% (◆).

Experiments performed in the absence of the secondary amine showed that, in contrast to Tsogoeva's observations in Mannich reactions, no enantioenrichment occurred and that simple mixing of **2** and **3** in DMSO did not lead to aldol product **1**. Both results suggested that the base was essential and that **1** did not catalyze its own retro-aldol reaction.[19]

In all cases, aldol product *anti*-**1** was accompanied by small quantities of the corresponding aldol condensation product, significant amounts of the *syn* diastereomer (ca. 30%) and traces of other stereoisomers of **1**. Use of piperidine instead of pyrrolidine avoided the formation of the condensation product.[20] Assuming that the *syn* product resulted from a low diastereoselectivity of the pyrrolidine- or piperidine-catalyzed aldol reactions, *rac*-proline was applied as organocatalyst instead. Starting from an initial imbalanced e.r. of 85:15, aldol product *anti*-**1** with an e.r. of 97.5:2.5 was obtained after 42 days (Figure 1). As hypothesized, less *syn* aldol product was formed, but apparently, the enantioenrichment was rather slow under those conditions. Finally, column chromatography allowed to isolate aldol product **1** with an *anti*/*syn* ratio of 80:20 and an e.r. of >99:1 for the major diastereomer in 87% yield.[21]

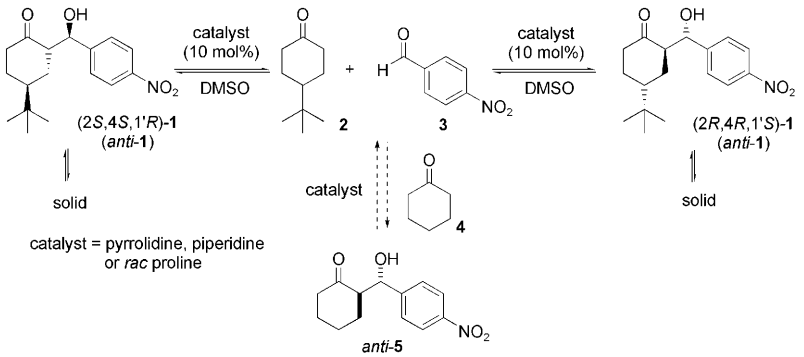
In order to confirm that the enantioenrichment involved the proposed retro-aldol reaction, a competition experiment with cyclohexanone (**4**) as co-reactant was performed (Scheme 2). Thus, in the presence of an excess of cyclohexanone (2.4 equiv) and with pyrrolidine as catalyst, 43% of *anti*-**1** (with an e.r. of 85:15) was converted into aldol product *anti*-**5** after six days. Interestingly, the e.r. of **1** was higher than without cyclohexanone (99:1). In contrast, *anti*-**5** was racemic, as expected.

That the current racemization conditions were favorable for the formation of racemic aldol product *anti*-**5** was also shown in an experiment starting from a solid–solution mixture of *anti*-**5** having an e.r. of 97:3 (in absence of **1**). As hypothesized, the e.r. decreased to give *anti*-**5** with a residual e.r. of only 54.5:45.5.[22,23]

In conclusion, we demonstrated that an aldol product that crystallizes as conglomerate can be enantiomerically enriched using a combination of crystal growth and iterative retro-aldol/aldol reactions. Considering the importance of aldol products in nature, these findings might have relevance for the development of biological homochirality.

Experimental Section

Typical procedure: Solid–solution mixtures of scalemic *anti*-**1** (120 mg; prepared by the addition of an appropriate amount of racemic *anti*-**1** to enantiomerically enriched samples) were magnetically stirred (800 rpm)



Scheme 2. Enantioenrichment of aldol product *anti*-**1** in presence cyclohexanone (**4**) as co-reactant.

in DMSO (50 μL) in presence of ZrO_2 beads (670 mg) as grinding medium. After establishing solid-solution equilibrium (30 min.), pyrrolidine (10 mol%) was added to provide racemization conditions in solution. Samples of the slurry were taken out over time and the e.r. of *anti*-**1** was determined by CSP-HPLC.

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Keywords: aldol reaction · asymmetric amplification · enantioenrichment · grinding · reversible reactions

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[20] Use of piperidine instead of pyrrolidine raised the e.r. of *anti*-**1** from 85:15 to 95:5:4.5 after 1 d. It reached an e.r. of 97.5:2.5 after 4 d.

[21] Although our results suggest that the enantioenrichment involves a deracemization through crystallization, we cannot, at the present stage, exclude that the e.r. is also affected by a selective destruction of the racemic compound in solution and/or its conversion into other stereoisomers. The latter hypothesis is supported by the results of the following experiments: Aldol products *anti*-**1** having 30 and 70% *ee* were heated in DMSO (to 60°C) until complete dissolution. Then, pyrrolidine was added to the solutions, and with intense stirring the mixtures were allowed to slowly cool to room temperature. Samples were taken from the resulting slurries and analyses by HPLC and ^{1}H NMR showed that 74 and 83%, respectively, of *anti*-**1** had been converted to the corresponding *syn*-aldol products. The stereochemical assignments of the resulting *syn*-**1** indicated unchanged *ee* values of 30 and 70%, respectively, and suggested that the major products had 2*R*,4*S*,1′*R*-configuration. These results can be interpreted as indication for a selective solution phase epimeriza-

tion of *anti*-**1** at C2 to give *syn*-**1**. Subsequent investigations of this interesting "destructive conversion" of stereoisomers in solution shall reveal to what extend this phenomenon is responsible for the observed e.r. change in the original experiments.

[22] Tsogoeva proposed that the enantiomerization process involved the formation of an enamine intermediate in solution and a chemisorption of the other reactant (in their case an imine) on the crystal surface of the major enantiomer (ref. [17b]). As a result, the major enantiomer is reproduced at the crystal/solution interface in an autocatalytic fashion. A racemic compound could reproduce itself in the same mode. It is not clear, however, how compound mixtures will behave. The formation of racemic *anti*-**5** in our competition experiments seems to indicate that the crystal surface of *anti*-**1** does not affect the stereochemical path of the *anti*-**5** formation.

[23] The reaction was conducted under the conditions of the competition experiment (with DMSO as solvent and 2.4 equiv of cyclohexanone). Without cyclohexanone, the *ee* was lower to give *anti*-**5** with a residual e.r. of 81.5:18.5.

[24] While this manuscript was under review, we learned about an organocatalytic asymmetric retro aldol reaction catalyzed by a chiral diamine triflic acid adduct which has been utilized in efficient kinetic resolutions (as reported by Professor Dr. S. Luo at Symposium on Catalysis and Fine Chemicals (C&FC) 2009 in Seoul on December 15, 2009). We thank Professor Luo for sending us subsequently an unpublished summary of his work.

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