Summary

Chiral purification of organic compounds is of paramount importance in the pharmaceutical industry but also in the food and agricultural industry. The homochirality of Nature leads to chiral recognition and the human body can distinguish between different enantiomers of chiral molecules. The consequence is sometimes a difference in taste or s mell, but in the most extreme cases it can imply the difference between death and cure. A chemical synthesis often results in a racemate that must be purified afterwards. One of the latest inventions for chiral purification is Viedma ripening. For that a racemic or scalemic mixture of conglomerate crystals is ground in contact with its saturated solution. In the solution a racemization reaction needs to be active. The solid phase in such a process evolves over time to an enantiomerically pure end state. Therefore Viedma ripening is a deracemization method rather than a resolution.

Viedma ripening requires that the compound crystallizes as a racemic conglomerate,

meaning that each crystal contains either (S) or (R) molecules. Unfortunately only around

10 % of all chiral organic compounds crystallize in this manner. The more abundant crystal

structure is a racemic compound where both enantiomers are part of the unit cell. Molecules

that crystallize in this way cannot be deracemized using Viedma ripening. The goal of the

research in this thesis was to find ways for also enantiomerically purifying such racemic

compounds.

The first example is the complete deracemization of the proteinogenic amino acid

glutamic acid (chapter 2). In the literature this compound is claimed to form a racemic

conglomerate, but the most stable crystal structure turns out to be that of a racemic

compound. We developed a method by exploiting Ostwald’s rule of stages and made use of a

metastable conglomerate crystal structure. Complete deracemization was possible by carefully tuning the experimental conditions before the conversion into the racemic compound occurred.

In the second example two racemic compound forming amino acids, alanine and

phenylalanine are studied (chapter 3). Both compounds can be transformed into stable

racemic conglomerates by screening for an appropriate salt. Benzene sulfonic acid salts

enabled a complete deracemization of both amino acids.

As alternative to the grinding method of Viedma ripening, a temperature cycling

approach was recently employed, by Coquerel et al.. Chapter 4 studies the applicability of this method for the two amino acid salts. The major question was whether the deracemization

would be faster using temperature cycling and what effect the various experimental conditions have on the deracemization rate. The deracemization of the amino acid salts using

temperature cycling was indeed faster.

Asparagine is one of the two proteinogenic amino acids that forms a racemic

conglomerate and thus appears suitable for normal Viedma ripening. The crystal structure,

however, is not stable under the racemization conditions for amino acids and a different route

is needed. Purification of this compound can be conducted by coupling two Viedma ripening

setups with small initial enantiomeric excess in the L and D enantiomer respectively and

without racemization in the solution (chapter 5). The solution is exchanged, crystal free,

between the two vessels and the solid phase of the slurry evolved to 100 % enantiomerical

purity. In the end one vessel contained only the L and the other only the D enantiomer.

Another possibility of converting a racemic compound into a racemic conglomerate is

derivatization. N-Acetyl-leucine is a derivative of the proteinogenic amino acid leucine.

Although it forms a stable conglomerate and is racemizable, the deracemization of this

compound did not proceed as expected (chapter 6). It is a good example to show the

importance of determining the yield during the development of a new Viedma ripening

application. During the deracemization experiments with the amino acids salts a persistent reverse enantiomeric excess in the solution was found that is unexpected based on existing models for Viedma ripening. Chapter 7 therefore presents an extended model that involves

thermodynamical clusters and indeed explains this phenomenon.