Invited Lecture

Crystallisation routes for deracemization

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There are several routes to produce compounds of single chirality, i.e. enantiopure molecules. Ever since the days of Pasteur, crystallisation has been a very important route. Here we discuss recent, crystallisation-based methods that allow complete deracemization, thus methods in which the unwanted compound is converted into the desired one and that can lead to 100% chiral purity and 100% yield. These are in particular Viedma ripening (Figure 1) [1] and temperature cycling [2]. These methods can also be combined with the more classic routes of diastereomeric resolution [3] and total spontaneous resolution [4].

The current understanding of the mechanism of these methods will be discussed as well as the conditions that need to be satisfied to apply these methods on a particular compound. The crystallization-based deracemization methods are typically not directly suitable for most compounds, but with enough effort a large number of interesting compounds can be made suitable, as was for example shown for the antimalarial drug Mefloquine [5].

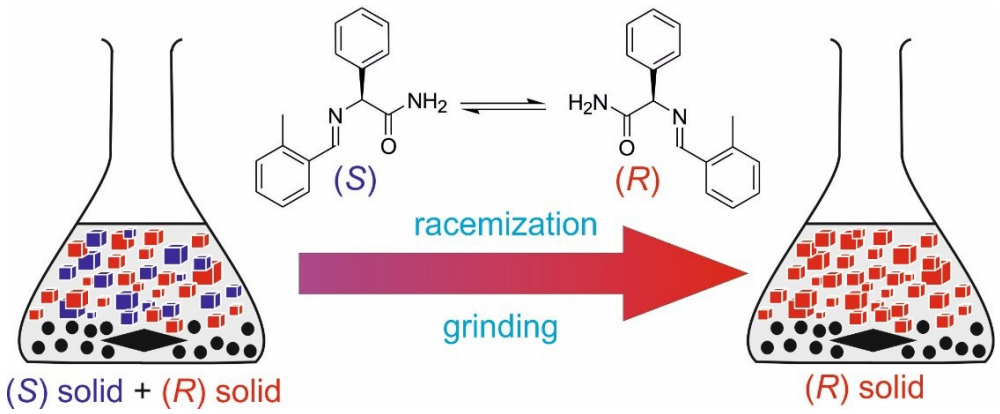

Figure 1. In Viedma ripening, a slurry of a racemic conglomerate crystals is converted to a single chirality by grinding and racemization in solution.

[1] C. Viedma (2005), *Phys. Rev. Lett*. **94** 65504; W.L. Noorduin et al. (2008) *J. Am. Chem. Soc.* **130**, 1158.

[2] K. Suwannasang et al. (2013), *Cryst. Growth Des.* **13**, 3498.

[3] T. Lerdwiriyanupap et al. (2021), *Eur. J. Org. Chem.* **44**, 5975.

[4] R.R.E. Steendam et al. (2014), *Nat. Commun.* **5**, 5543.

[5] A.H.J. Engwerda et al, (2019) *Angew. Chem. Int. Ed.* **58**, 1670.