Invited Lecture

Chiral resolution through crystallization in mixed crystal systems based on heterogeneous equilibria

R. Oketani

Division of Chemistry, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan.

r.oketani.es@osaka-u.ac.jp

Access to chiral compounds is a crucial fundamental technology in industry, and among various methods, crystallization-based chiral resolution is an economically advantageous approach suitable for mass production. Classical methods such as preferential crystallization, diastereomer method, and the deracemization all require crystal structures where the desired isomer is contained in a single crystal, such as conglomerates or diastereomeric salt Therefore, solid solutions, which contain multiple isomers in non-stoichiometric proportions within the unit cell, are recognized as problematic. In this study, we introduce two new chiral resolution methods achieved by understanding phase diagrams for solid solutions[1-3]. The first method is deracemization utilizing solid solution in the conglomerate phase. The axially chiral compound pMe, shown in Figure 1a, forms a conglomerate, while the structurally similar pCl yields a racemic compound. Constructing a melting point phase diagram of the pMe/pCl system revealed that these two compounds form a partial solid solution. Deracemization by crystallization was performed at a mixing ratio that yields a conglomerate-type solid solution, successfully amplifying the chirality in the crystal phase (Figure 1a) [1]. The second method is crystallization-induced diastereomeric transformation (CIDT) of chiral primary amine compounds. The aminoindane derivative, an intermediate in the synthesis of the drug Ozanimod, and the tartaric acid derivative form a solid solution diastereomeric salt (Figure 1b). Although a single crystallization only achieves an insufficient chiral resolution of 24% diastereomeric excess (*de*), constructing a ternary isothermal phase diagram revealed a significant solubility difference between the diastereomers. Focusing on this difference, CIDT was performed with the addition of an Ir catalyst capable of racemizing the amine, resulting in the convergence of the *de* in solid phase to around 70-80. Interestingly, this composition is close to the solid solution limit of the diastereomers, suggesting a connection between the driving force of crystallization-based deracemization and the thermodynamic equilibrium state[2,3]. In this presentation, the phase diagrams for each system and chiral resolution by crystallizations will be discussed in detail.

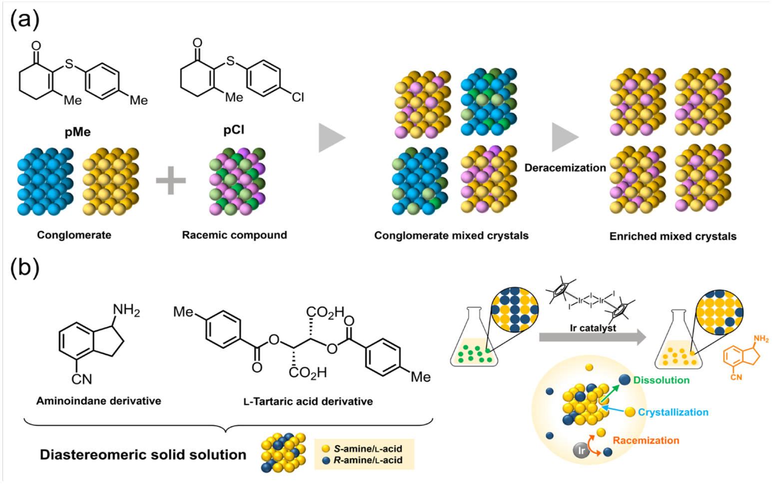

Figure 1. (a) Deracemization of the mixed crystal system composed of pMe/pCl. (b) CIDT of the diastereomeric solid solution system composed of the aminoindane derivative and the L-tartaric acid derivative.

[1] Pinètre, C., Gendron, F.-X., Kuroda, R., Oketani, R., Aupetit, C., Buffeteau, T., Coquerel, G. (2023). *Chem. Eur. J.*, e202300441.

[2] Oketani, R., Shiohara, K., Hisaki, I. (2023). *Chem. Commun.*, **59**, 6174.

[3] Oketani, R., Shiohara, K., Hisaki, I. (2024). *ChemRxiv*, DOI: 10.26434/chemrxiv-2024-rmkk7.

Thes works were supported by CORE project of the European Union under a Marie Sklodowska-Curie grant agreement (No.722456), KAKENHI (JP21K20534, 23K13708, 23H04593, and 21H01919) from JSPS, a project JPNP20004 by NEDO, and JST ACT-X (JPMJAX22A2), and Sasakawa Scientific Research Grant (No. 2023-3021) from The Japan Science Society.