"*Solvent-Induced Chirality Switching*" in the Enantioseparation of Chlorine-Substituted Tropic Acids via Diastereomeric Salt Formation

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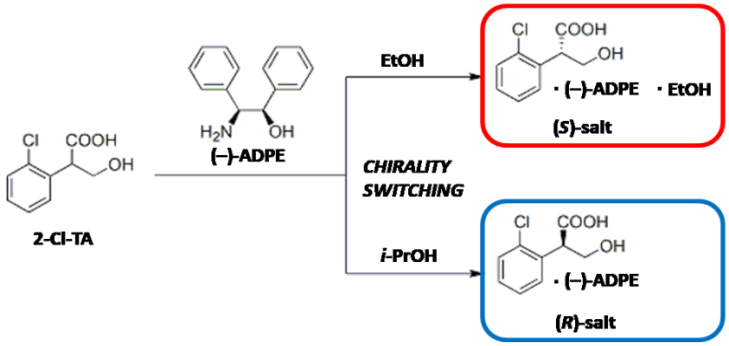
The optical resolution via diastereomeric salt formation is a widely employed method for obtaining optically pure acidic and basic compounds on an industrial scale. In this method, a target racemate is combined with an optically active resolving agent and enantioseparation is enabled by crystallization. ***'Solvent-induced chirality switching resolution'*** is a phenomenon in which the stereochemistry of a less-soluble diastereomeric salt changes depending on the solvent used for crystallization in optical resolution by diastereomeric salt formation. Optically pure tropic acid (TA) and its derivatives are important compounds for the production of pharmaceuticals. Among the TA derivatives reported to date, enantiopure chlorine-substituted TA is an important chiral building block of hyoscyamine derivatives.

Previously, we reported solvent-induced chirality switching during the optical resolution of racemic TA using (–)-ADPE.[1] To expand the scope of solvent-induced chirality switching resolution, herein we demonstrate an efficient solvent-induced chirality switching resolution of racemic 2-chlorotropic acid (*rac*-2-Cl-TA) with (–)-ADPE via diastereomeric salt formation. The recrystallization of the diastereomeric salts of *rac*-2-Cl-TA from branched alcohols such as *i*-PrOH and *s*-BuOH afforded (*R*)-2-Cl-TA, whereas (*S*)-2-Cl-TA was obtained from linear alcohols such as MeOH, EtOH, and *n*-PrOH. The chirality switching mechanism was elucidated from the crystal structures of the diastereomeric salts, which revealed that the incorporation of the solvent in the (*S*)-2-Cl-TA salt crystals played a key role in chirality switching by reinforcing the supramolecular structure of the salt. However, no chirality switching was achieved for racemic 3-chlorotropic acid and 4-chlorotropic acid. The position of the chlorine substituent plays an important role in the solvent-induced chirality switching effect.



1) K. Kodama, N. Kurozumi, H. Shitara, T. Hirose, *Tetrahedron*, **2014**, *70*, 7923.