Solvent-induced chirality switching effect in the enantioseparation of 2-chlorotropic acid by (1*R*,2*S*)-(—)-2-amino-1,2-diphenylethanol

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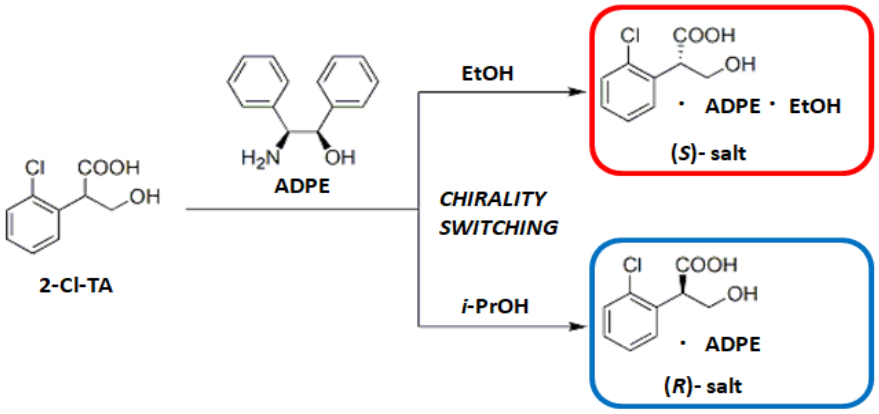
Keywords:Optical Resolution; Diastereomeric Salt Formation; Solvent-induced Chirality Switching; 2-Chlorotropic Acid; Crystal Structures

'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.[1] Among the tropic acid (TA) derivatives reported to date, chlorine-substituted TA is important as it can be further easily functionalized into other TA derivatives by cross coupling reactions. Enantiopure 2-chlorotropic acid (2-Cl-TA) is significant as a chiral building block of hyoscyamine derivatives. It is widely known that (*R*)-hyoscyamine exhibits analgesic activity whereas (*S*)-hyoscyamine is an antagonist of muscarinic receptor.[2]

In order to expand the scope of solvent-induced chirality switching resolution, 2-Cl-TA has been selected as a target chiral carboxylic acid in this research work. Herein, we have demonstrated an efficient solvent-induced chirality switching effect in the optical resolution of 2-Cl-TA with (1*R*,2*S*)-(—)-2-amino-1,2-diphenylethanol (ADPE) via diastereomeric salt formation that enabled access to both its enantiomers simultaneously. The salt of (*R*)-2-Cl-TA was obtained from THF and branched alcohols such as *i*-PrOH and *s*-BuOH whereas the linear alcohols such as MeOH, EtOH and *n*-PrOH afforded the salt of (*S*)-2-Cl-TA. The crystallographic analysis revealed that the solvent inclusion in the salt crystals of (*S*)-2-Cl-TA played a key role in chirality switching by reinforcing the supramolecular structure of the salt.



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