Development of Novel Methods for Production of Chiral Heterocyclic Compounds by Using Kinetic Resolution of Racemic Compounds
（速度論的光学分割法を用いたキラルなヘテロ環状物質の新規不斉合成法の開発）

1. Introduction

Molecular chirality is a fundamental property of nature and is of central importance in chemistry and biochemistry; thus, the stereochemical control is a major challenge in the synthesis of biologically active compounds such as natural products, pharmaceuticals, and agricultural chemicals. Among various approaches to obtain chiral compound, the catalytic kinetic resolution (KR) and dynamic kinetic resolution (DKR) of racemates is one of the most economical solutions.

Prof. Shiina has previously reported a series of KR and extended them to powerful DKR which consists of a rapid racemization step via substrate activation and an enantio-discrimination step via catalytic esterification. As a part of continuing studies on KR via asymmetric esterification, we have focused on expansion of application areas especially hetero compounds for being more practical. Although a number of useful catalytic KR protocols have already reported, there has yet, to the best of our knowledge, no example of a catalytic KR system for protected $\alpha$-amino acids ($\alpha$-AAs) and 2-hydroxyacetals via direct esterification using acyclic precursors. Consequently, it is still highly desirable to develop more general system which includes a broad scope of substrates with mild reaction conditions. In the following contents, the novel DKR for producing chiral $\alpha$-AAs and the first KR for production of chiral 2-hydroxyacetals are described.

2. Development of novel dynamic kinetic resolution for producing chiral $\alpha$-amino acids

Alpha-AAs have long been known to play crucial roles in organic chemistry, and the enantio-controlled and catalytic construction of the chiral $\alpha$-position of $\alpha$-AA has been targeted as

![Scheme 1. Development of novel DKR for producing chiral $\alpha$-amino acids.](image-url)
an attractive synthetic goal. Based on the previous investigation, we hypothesized that the substrate scope of this mild mixed-anhydride procedure could broaden; on the other hand, rapid racemization of substrate bearing amino group at \( \alpha \)-position seemed to be challenging since the electron-rich amine decreases the \( \alpha \)-proton acidity. Throughout the exploration, we finally found that pyrrolyl protective group was the key to success of the transformation. Here, the first nonenzymatic metal-free DKR of racemic \( N \)-protected \( \alpha \)-AA derivatives is presented.

3. Practically established dynamic kinetic resolution of racemic \( \alpha \)-amino acids

In the initial study as mentioned above, the desired resolution of \( \alpha \)-AA analogs was achieved, albeit with insufficient efficiencies. Having investigated various reaction facets and mechanism of stereoselectivity by density functional theory (DFT) calculations, we herein report generality and effectiveness of the DKR system. Moreover, further application with demonstration by the short synthesis of the indolizidine alkaloid scaffold was explored.

4. Kinetic resolution of racemic 2-hydroxyacetals\(^3\)

Optically active 2-hydroxyacetal derivatives are versatile building blocks of various biologically active compounds. However, a general chemical KR of these compounds has not yet been reported.

Screening of acetal moieties led us to identify 5-membered cyclic acetals with high \( s \)-values. We also examined the reaction conditions optimization, and found that use of ether as a solvent afforded better result than other solvents. In addition, the reaction transition states were elucidated using theoretical calculations; it was clarified that 1,3-dioxolane is a suitable reagent for attaining high selectivity.