Hydrogenative Dynamic Kinetic Resolution of α-Substituted α-Amino Esters Catalyzed by Ru(II) Complexes

([1]*Graduate School of Chemical Sciences and Engineering, Hokkaido University*, [2] *Division of Applied Chemistry, Faculty of Engineering, Hokkaido University,* [3] *Frontier Chemistry Center, Hokkaido University*) ○ Mingyuan Gao[1], Ryou Komatsu[1], Noriyoshi Arai[2], Takeshi Ohkuma[2,3]

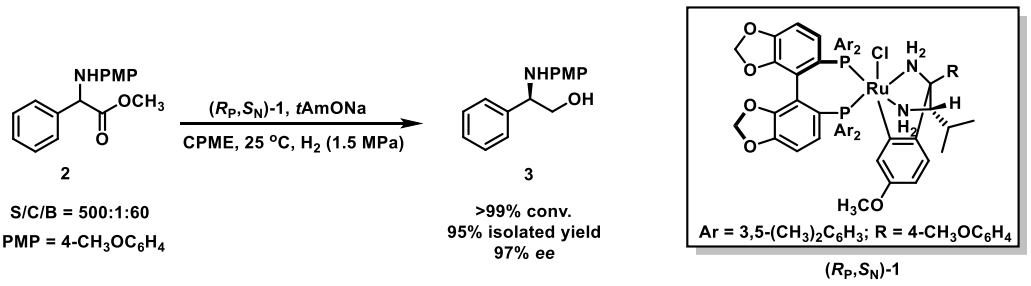
Keywords: Dynamic kinetic resolution, Ruthenium catalysis, Hydrogenation, Asymmetric synthesis, β-Aminoalcohols

Catalytic asymmetric reactions are indispensable methodologies for the efficient synthesis of organic compounds with high stereoselectivity.[1] After the thalidomide incident, the pharmaceutical industry began to pay attention to the asymmetric synthesis of drugs. Chiral β-amino alcohols are ubiquitous in natural products and serve as an important type of building block for the synthesis of many pharmaceutical and agrochemical substances. Optical resolution of the corresponding α-amino acid is an elegant and efficient method for obtaining optically active amines, however the yield of desired compound is less than 50%.

Dynamic kinetic resolution (DKR) is a type of kinetic resolution where 100% of a racemic compound can be converted into an enantiopure compound in theory.[2] Therefore, if it is applied to the synthesis of optically active β-amino alcohols by asymmetric hydrogenation, it will be challenging and efficient.

The RUCY-SEGPHOS-type Ru-catalyzed hydrogenation allows efficient dynamic kinetic resolution of certain α-substituted α-amino esters to lead to the β-amino alcohols in high enantiomeric excesses.

After screening the conditions, the α-amino acid esters **2** can be smoothly converted to the corresponding β-amino alcohols **3** under the following conditions. When (R_P,S_N)-**1**[3] was used as the complex and *t*AmONa as the base, the product was obtained in 95% isolated yield and 97% *ee* at 25 °C with 1.5 MPa of hydrogen gas. This method achieves mild conditions, high yield, and enantioselectivity, and is suitable for scale-up with potential industrial applications.



1) Ohkuma, T.; Kurono, N.; Arai, N. *Bull. Chem. Soc. Jpn.* **2019**, *92*, 475–504. 2) El, G. M. T.; Williams, J. M. *J. Curr. Opin. Chem. Biol.* **1999**, *3*, 11–15. 3) Matsumura, K.; Arai, N.; Hori, K.; Saito, T.; Sayo, N. and Ohkuma, T. *J. Am. Chem. Soc*. **2011**, *133*, 10696–10699.