27O-ISMS31 **Development of Highly Stereoselective Synthetic Method for 3-amino-4-hydroxytetrahydropyran via Transfer Hydrogenation**

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Highly stereoselective synthetic method of 3-amino-4-hydroxytetrahydropyran, a key fragment of some active pharmaceutical ingredients (APIs), has been developed. This synthetic method consists of three key reactions, following with process optimization;

1) **Neber rearrangement:** In order to improve the reaction yield, it was important to suppress the decomposition of the raw material having poor thermal stability. In the first step of the rearrangement, the issue of decomposition was avoided by low reaction temperature (0 ºC). Then, α-amino cyclic ketone which was a target substrate of asymmetric reduction was obtained in good yield.
2) **Dynamic kinetic asymmetric transformation by transfer hydrogenation:** Dynamic kinetic asymmetric transformation to *cis*-α-amino cyclic alcohol was established with extremely high enantioselectivity. The commercially available chiral catalyst, [RuCl(*p*-cymene){(*R*,*R*)-Tsdpen}], was used under low amount of catalyst loading for this reaction.
3) **Stereo inversion of hydroxy group by S_N2 reaction:** The S_N2 reaction could be carried out using inexpensive reagents such as acetic acid and DBU, and the desired *trans*-α-amino cyclic alcohol was obtained without epimerization.

Based on the developed synthetic method, 15 kg of (3*S*,4*S*)-3-amino-4-hydroxytetrahydropyran have been obtained in a total yield of 37%.

In addition, application of our synthetic procedure has enabled to afford all four kinds of stereoisomers (a target configuration substance, its enantiomer, and its diastereomers of α-amino cyclic alcohol) by using [RuCl(*p*-cymene){(*R*,*R*)-Tsdpen}] or [RuCl(*p*-cymene){(*S*,*S*)-Tsdpen}].