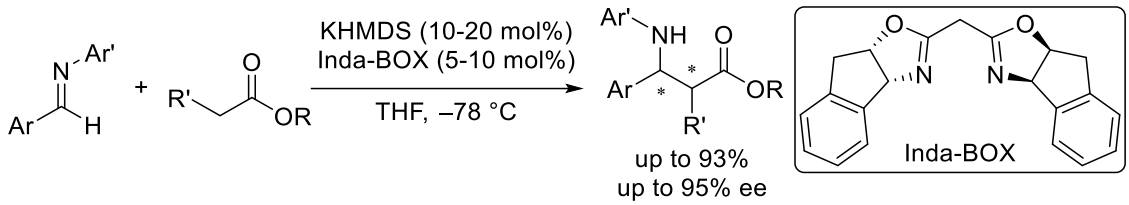
Development of Catalytic Enantioselective Mannich Reactions of Esters and Effective Transformations of the Mannich Adducts toward Asymmetric Synthesis of β-Lactams

(School of Science, The Univ. of Tokyo) ○ Seiya FUSHIMI, Tomoya KIMURA, Yasuhiro YAMASHITA, Shū KOBAYASHI

Keywords: Strong Base Catalysis; Asymmetric Mannich Reaction; Simple Ester; Oxidative *N*-aryl Bond Cleavage Reaction; *β*-Lactam Synthesis

Asymmetric Mannich reactions of esters are one of the important methods to synthesize optically active *β*-amino esters. These types of reactions have been conducted in the presence of chiral Lewis acid catalysts using ketene silyl acetals prepared from esters beforehand, or they have been conducted with stoichiometric amounts of strong Brønsted bases. However, catalytic asymmetric direct Mannich reactions using simple esters such as acetates, propionates, *etc.* without any electron-withdrawing groups at their *α*-positions have been difficult because *α*-hydrogen atoms of such esters are generally too weakly acidic to be promoted by typical chiral Lewis acid/Brønsted base catalysts. On the other hand, our group has developed catalytic direct addition reactions of simple esters by using a strong base catalyst, where strongly basic intermediates of the reactions were designed.[1,2] However, asymmetric addition reactions of simple esters have been still difficult and limited.[3] Recently we found that chiral potassium salts, formed by the deprotonation of chiral bisoxazoline (BOX) ligands and potassium hexamethyldisilazide (KHMDS), significantly accelerated Mannich reactions of weakly acidic simple amides.[4] Interestingly, this acceleration also occurred when simple esters were employed, and undesired side-reactions of acetates were suppressed. Here, we report the development of catalytic asymmetric direct Mannich reactions of simple esters with *N*-arylimines. The desired adducts were obtained in good yields with high enantioselectivities. Further transformations of the Mannich adducts were successfully performed.



1) S. Kobayashi *et al. Org. Biomol. Chem.* **2012**, *10*, 5750. 2) S. Kobayashi. *et al. Synlett* **2021**, *32*, 14. 3) S. Kobayashi *et al. Org. Chem. Front*. **2016**, *3*, 124. 4) S. Kobayashi *et al. J. Am. Chem. Soc.* **2021**, *143*, 5598.