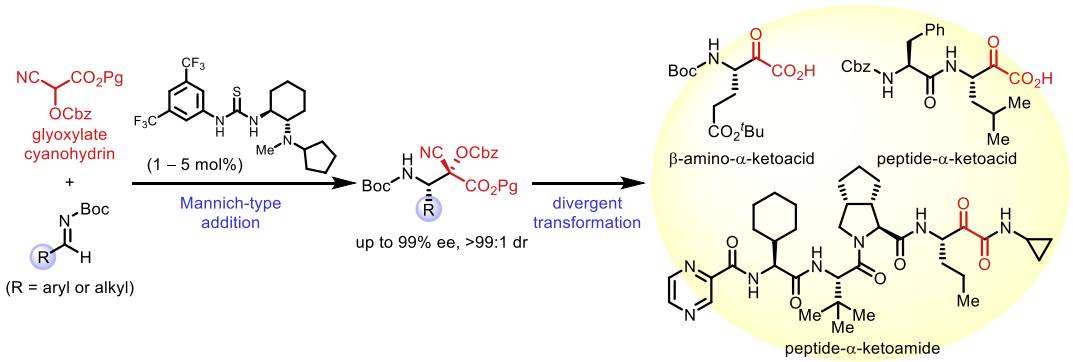
Asymmetric Preparation of β-Amino-α-ketoacids by the Highly Stereoselective Mannich-type Addition for the Peptide Synthesis

(*Graduate School of Pharmaceutical Sciences, Kyoto University*) ○Yusuke Tokuhiro, Kosuke Yoshikawa, Sei Murayama, Takeshi Nanjo, Yoshiji Takemoto

Keywords: β-Amino-α-ketoacid; Mannich Reaction; Organocatalysis; Asymmetric Synthesis; Peptide

β-Amino-α-ketoacids are important unnatural amino acids featured by an unique bioactivity and reactivity derived from a highly electrophilic carbonyl group at α-position. Despite of the broad utility of the motif, a reliable synthetic method of β-amino-α-ketoacids has been limited to oxidative homologation of α-amino acids based on chiral pool approach.[1] In addition, elongation of peptide chains for the synthesis of bioactive compounds requires an appropriate protection or late-stage installation of α-carbonyl group to avoid undesired reactivity.

In order to establish a novel approach providing a wide variety of β-amino-α-ketoacids and their peptide derivatives, we envisaged that asymmetric Mannich-type addition of glyoxylate cyanohydrin to imines would afford the equivalent of β-amino-α-ketoacids. As a result of catalyst screening, we found that sterically-tuned aminothiourea catalyst provided the desired adducts bearing variable residue including non-proteinogenic one with excellent enantio- and diastereoselectivity.[2,3] The asymmetric adducts are readily converted to β-amino-α-ketoacids by simple two-step operations. We also achieved the divergent transformation from the Mannich adducts to peptide-α-ketoacids and peptide-α-ketoamides by utilizing the cyanohydrin motif at α-position as an easily removable protecting group, and demonstrated the synthetic utility in decarboxylative peptide fragment coupling and preparation of α-ketoamide-containing pharmaceutical.



1) Ju, L.; Lippert, A. R.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 4253.
2) Nanjo, T.; Zhang, X.; Tokuhiro, Y.; Takemoto, Y. *ACS Catal.* **2019**, *9*, 10087.
3) Tokuhiro, Y.; Yoshikawa, K.; Murayama, S.; Nanjo, T.; Takemoto, Y. Manuscript in preparation.