Carbonyl catalysis enables a biomimetic asymmetric Mannich reaction

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Zhao Baoguo (赵宝国) at the Education Ministry Key Lab of Resource Chemistry and Shanghai Key Laboratory of Rare Earth Functional Materials, Shanghai Normal University, recently reported the chiral pyridoxal-catalyzed biomimetic asymmetric Mannich reaction, which was published in *Science* (2018, 360: 1438—1442).

Organocatalysis has boomed into one of the most important research fields in organic chemistry over the past decade. Carbonyl compounds are a type of significant and highly available organic molecules, however, they are barely employed as catalysts for synthetic transformations. Inspired by the L-threonine aldolase-promoted aldol reaction of glycine, Zhao and coworkers proposed a carbonyl catalysis mode for direct α-functionalization of primary amines (Figure A). A primary amine can be activated by a carbonyl catalyst via imine intermediate, promoting the formation of an α-amino carbanion to react with an electrophile to produce an α-substituted amine.

As inspired by threonine aldolase and also based on their previous studies on biomimetic chemistry of vitamin B_6, Zhao and coworkers developed *N*-methyl biary axially chiral pyridoxal (Figure B). By using the chiral pyridoxal as a carbonyl catalyst, the group successfully realized biomimetic asymmetric Mannich reaction of glycinate with *N*-diphenylphosphinyl imines, to produce various α,β-diamino acid esters in good to high yields with excellent diastereo- and enantioselectivities (Figure C). α, β-Diamino acids are synthetically useful and biologically important and are widely present in many biologically active compounds such as drugs Lavendomycin and Roxifiban. This work has provided an efficient and highly selective method for the synthesis of α,β-diamino acids, and also successfully demonstrated the carbonyl catalysis mode to α-functionalize primary amines without extra protecting manipulation towards the NH_2 group.

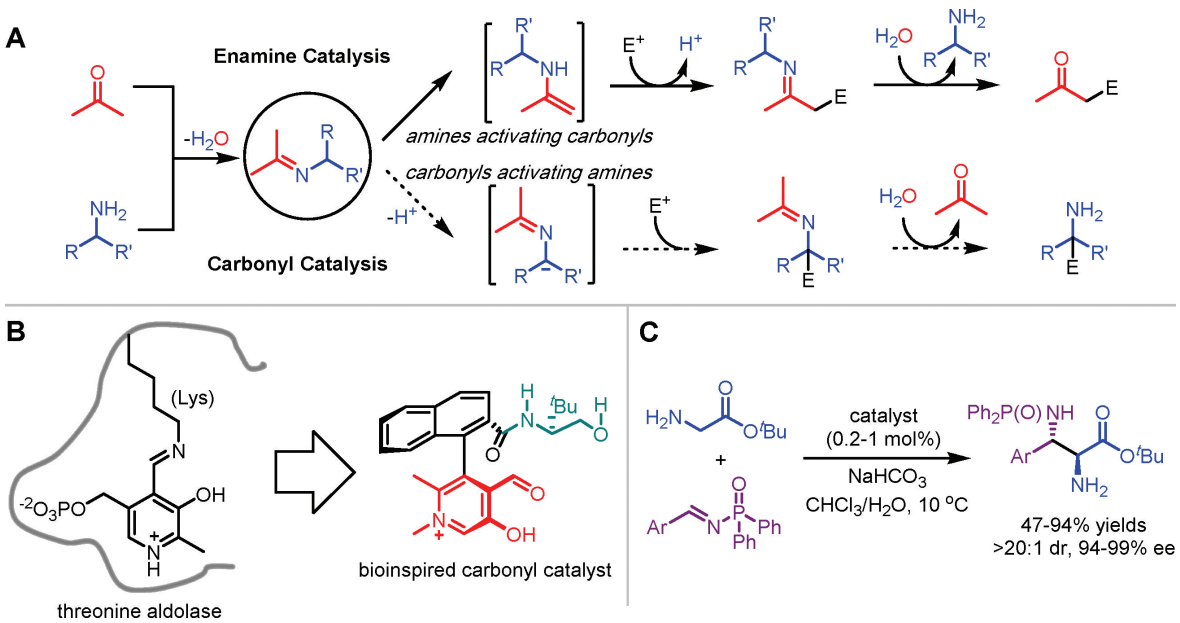

Figure (A) Carbonyl catalysis vs enamine catalysis; (B) bioinspired carbonyl catalyst; (C) asymmetric biomimetic Mannich reaction.