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A biomimetic breakthrough in glycinate aldol reaction: Enzyme-inspired efficient access to chiral β-hydroxy-α-amino acids

Haifeng Du[1,2,*]

[1]Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, CAS, Beijing 100190, China

[2]University of Chinese Academy of Sciences, Beijing 100049, China

*Correspondence: haifengdu@iccas.ac.cn

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Products generated via biocatalysis often inherit high and precisely defined bioactivity from their enzymatic origins. Threonine aldolase (TA) epitomizes this principle: by coupling glycine with aldehydes, it yields chiral β-hydroxy-α-amino acids—privileged motifs prevalent in marketed drugs, natural products, and potent lead compounds.[1] However, general access to these targets has long been hindered by TA's narrow substrate tolerance, persistent challenges in β-carbon stereocontrol and the lack of effective chemosynthetic methods. Recently, Zhao, Xiao, and their coworkers reported the first catalytic enantioselective biomimetic aldol reaction of glycinate, addressing a decades-old challenge and establishing an operationally simple, general route to chiral β-hydroxy-α-amino acid derivatives.[2]

The authors faced three longstanding problems that had long prevented catalytic glycine aldol reactions: first, the reaction is reversible, leading to product breakdown via retro-aldol cleavage; second, products tend to epimerize under pyridoxal conditions; third, aldehydes and glycine can form imines that block the aldol step. To tackle these, they designed a chiral pyridoxal catalyst with a squaramide side chain—this molecule integrates several enzyme-like functions, including covalent activation, hydrogen-bond cooperation, and selective substrate binding. Its biaryl backbone and side chain create a chiral pocket that holds aldehyde in the proper orientation, while the pyridoxal part forms a reversible imine with glycine ester. This activation of the α-C–H bond then enables controlled C–C bond formation.

The performance of biomimetic catalysis is impressive. Aromatic, heteroaromatic, and aliphatic aldehydes all react efficiently, affording β-hydroxy-α-amino acid esters in high yield and excellent selectivity (up to > 20:1 dr and > 99% ee). Electronic effects have little impact on the reaction: both electron-rich and electron-poor aldehydes proceed smoothly, highlighting the catalyst's broad utility. Its synthetic applications are immediately apparent. Key fragments present in antibiotics (thiamphenicol, florfenicol, chloramphenicol, vancomycin), metabolic drugs (eliglustat), natural products (lactacystin, dihydrosphingosine), and other bioactive molecules can be accessed directly. Notably, with a 0.01 mol% catalyst loading, a critical intermediate of florfenicol, L-threo-*p*-(methylsulfonyl)phenylalanine ester, was obtained in 82% yield, 15:1 dr, and 98% ee in a single step. The anti-Parkinson's drug droxidopa was also prepared in just two steps. Compared with traditional methods, this biomimetic route eliminates resolution and protecting

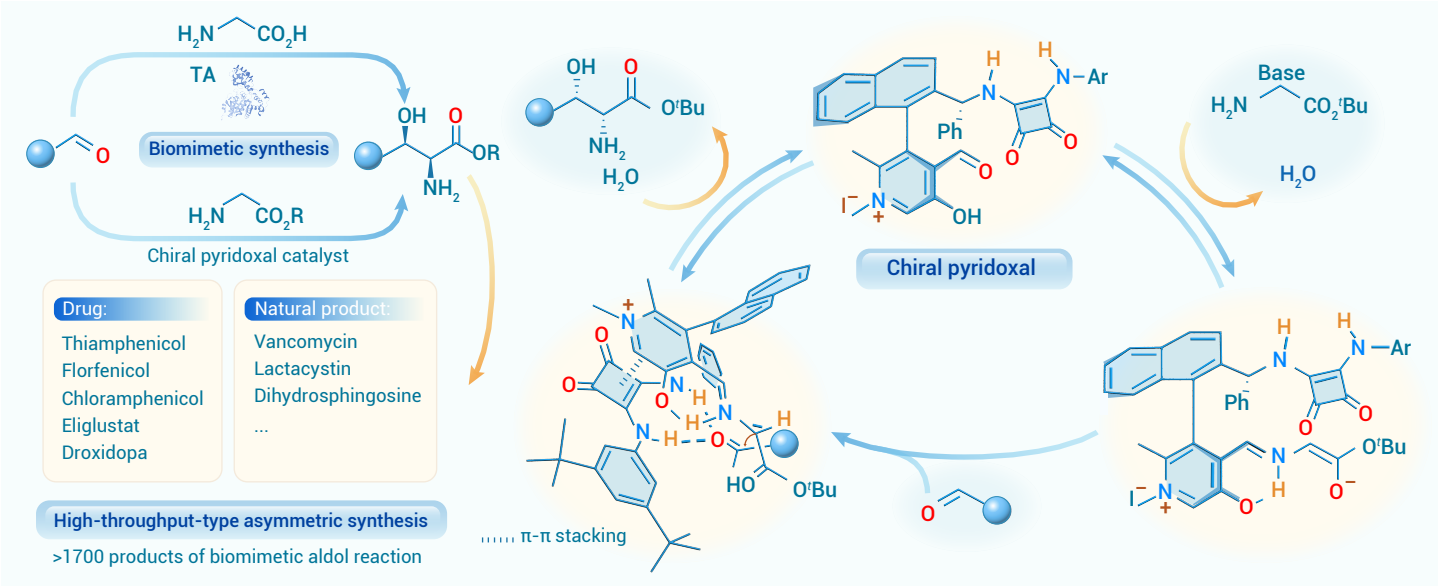

Figure 1. Mechanism diagram of biomimetic glycinate aldol reaction.

group steps, shortens the synthesis, reduces costs, and is more environmentally friendly. Additionally, the aldol adducts serve as versatile building blocks, which can be easily converted into a variety of chiral molecules.

The transformation closely mirrors the enzymatic logic of threonine aldolase (TA) (Figure 1). The pyridoxal moiety forms an imine with the glycine ester, enabling α-deprotonation to generate a delocalized carbanion which then adds to the aldehyde enantioselectively. Subsequent hydrolysis releases the β-hydroxy-α-amino acid ester and regenerates the catalyst. The squaramide-derived hydrogen-bond network precisely activates the carbonyl substrate, while the biaryl scaffold and side chain construct a chiral cavity that regulates both reactivity and stereochemical outcomes. This integration of covalent activation, dual hydrogen-bond cooperativity, and pocket-level substrate recognition yields a striking small-molecule mimic of the orchestrated interactions within an enzyme's active site.

The approach is highly scalable for drug discovery applications. By leveraging high-throughput-type asymmetric synthesis, the team constructed a library of over 1,700 β-hydroxy-α-amino acid esters. Despite significant substrate diversity, most library members were obtained with high conversion and stereoselectivity. Notably, the products typically required only minimal workup and no chromatographic purification—an attractive attribute for rapid bioactivity screening. Such a large dataset will be of great value for advancing AI-driven chemistry and accelerating the discovery of bioactive

molecules in the future.

Zhao, Xiao, and their coworkers have developed a conceptually elegant and practically powerful surrogate for TA chemistry. Their catalyst matches and in some aspects even surpasses enzymatic benchmarks in activity and selectivity, while retaining the tunability inherent to small-molecule design. Beyond providing broad access to β-hydroxy-α-amino acids for medicinal chemistry, this study underscores the growing potential of bioinspired catalysis: by distilling the essential elements of enzymatic function into compact molecular architectures, it delivers scalable, general solutions to challenges that have stymied both biological and traditional synthetic approaches.[3] While threonine aldolase and its variants remain valuable biocatalysts, with intrinsic advantages such as high biocompatibility and innate selectivity, this contribution clearly sets a new standard for biomimetic catalysis.[4,5] It demonstrates that rationally designed small molecules can not only rival but also complement enzymatic systems, offering a robust, general, and practical route that had long eluded the field.

Moreover, the integration of these valuable asymmetric high-throughput synthesis data with machine-learning-guided catalyst design will further advance the capabilities of biomimetic systems, accelerating the development of modular, tunable, and scalable catalytic platforms. This work will resonate across catalysis, drug discovery, and synthetic biology, and establishes a landmark reference point for future biomimetic transformations.

REFERENCES

1. Dückers N., Baer K., Simon S., et al. (2010). Threonine aldolases—screening, properties and applications in the synthesis of non-proteinogenic β-hydroxy-α-amino acids. *Appl. Microbiol. Biotechnol.* **88**:409. DOI:10.1007/s00253-010-2751-8
2. Liang H., Ren P., Wang L., et al. (2025). Asymmetric biomimetic aldol reaction of glycinate enables highly efficient synthesis of chiral β-hydroxy-α-amino acid derivatives. *Nat. Catal.* **8**:668. DOI:10.1038/s41929-025-01364-z
3. Breslow R. (1995). Biomimetic Chemistry and Artificial Enzymes: Catalysis by Design, *Acc. Chem. Res.* **28**:146. DOI:10.1021/ar00051a008
4. Xiao X. and Zhao B. (2023). Vitamin B6-based biomimetic asymmetric catalysis. *Acc. Chem. Res.* **56**:1097. DOI:10.1021/acs.accounts.3c00053.
5. Xiao X., Xu K., Gao Z.-H., et al. (2023). Biomimetic asymmetric catalysis. *Sci. China Chem.* **66**:1553. DOI:10.1007/s11426-023-1578-y

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The author declares no competing interests.