Asymmetric biomimetic transamination of $\alpha$-keto amides to peptides

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Peptides are important compounds with broad applications in many areas. Asymmetric transamination of $\alpha$-keto amides can provide an efficient strategy to synthesize peptides, however, the process has not been well developed yet and still remains a great challenge in both enzymatic and catalytic chemistry. For biological transamination, the high activity is attributed to manifold structural and electronic factors of transaminases. Based on the concept of multiple imitation of transaminases, here we report N-quaternized axially chiral pyridoxamines 1 for enantioselective transamination of $\alpha$-keto amides, to produce various peptides in good yields with excellent enantio- and diastereoselectivities. The reaction is especially attractive for the synthesis of peptides made of unnatural amino acids since it doesn’t need great efforts to make chiral unnatural amino acids before amide bond formation.

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Peptides are one type of the most important compounds with high biological activities, which are widely present in many natural products, pharmaceutically relevant molecules, and biological systems. Especially in recent years, there appears a growing interest in therapeutic peptides and more and more peptide drugs have been developed. Development of alternative new methods for the synthesis of peptides is always highly desirable and potentially useful.

Enzymatic transamination is an important process to produce chiral amines such as amino acids in biological systems, which is promoted by transaminases with pyridoxal/pyridoxamine 5′-phosphates as the coenzyme. Mimicking the biological process, i.e., asymmetric biomimetic transamination, affords the key step of biological transamination: asymmetric 1,3-proton shift.

**Fig. 1 Peptides and transamination.** a Peptide drugs. b Biological transamination. c Catalyst design. d 1,3-Proton shift. e Transamination of α-keto amides.
a highly intriguing method to synthesize NH2-free amines from readily available carbonyl compounds. The chemistry has attracted much attention since the 1970s. The studies mainly include stoichiometric chiral pyridoxamine-promoted asymmetric transamination of $\alpha$-keto acids, pyridoxal/pyridoxamine-catalyzed asymmetric transamination of $\alpha$-keto acids, and chiral Lewis acid-catalyzed asymmetric transamination of $\alpha$-keto esters and activated ketones. Although the reverse process, transamination of peptides at the N-termini to $\alpha$-keto amides, has been widely developed and already have been successfully applied to protein modification. In contrast to the transamination of $\alpha$-keto acids, asymmetric transamination of $\alpha$-keto amides to peptides remains a challenge for enzymatic catalysis likely due to non-naturally occurring process and it is also a challenge for chemical catalysis probably because the complicated structure of $\alpha$-keto amides requires more active catalysts to promote transamination.

Previous studies have suggested that asymmetric 1,3-proton shift between the ketimine intermediate and the aldmine is likely a key step for biological transamination. However, to the best of our knowledge, asymmetric transamination of $\alpha$-keto amides to peptides are barely reported, although the reverse process, transamination of peptides at the N-termini to $\alpha$-keto amides, has been widely developed and already have been successfully applied to protein modification. In contrast to the transamination of $\alpha$-keto acids, asymmetric transamination of $\alpha$-keto amides to peptides remains a challenge for enzymatic catalysis likely due to non-naturally occurring process and it is also a challenge for chemical catalysis probably because the complicated structure of $\alpha$-keto amides requires more active catalysts to promote transamination.

Here we show that asymmetric biomimetic transamination of $\alpha$-keto amides can be achieved by using chiral pyridoxamines as the catalyst, to produce various peptides with excellent enantioselectivities.

**Condition optimization.** With diphenylglycine (4) as the amine source, catalyst chiral pyridoxamine 1b was first tested for the transamination of glycinal $\alpha$-keto amide 2a (Fig. 3, entry 1). The originally-formed NH2-free transamination product was treated with di-tert-butyl dicarbonate to avoid the cyclization to piperazinedione during the isolation, to give the corresponding N-Boc-protected dipeptide 3a in 20% yield with 76% ee. Additives have significant impacts on the reaction in terms of enantioselectivity and activity. Increased yield and enantioselectivity were obtained for transaminations performed in MeOH/H2O or TFEA/H2O with HOAc/KOAc or HOAc/Na2HPO4 as the additives (Fig. 3, entries 2 and 10 vs 3–9). Chiral pyridoxamine 1b exhibited the best performance among the catalysts 1a–e examined (Fig. 3, entries 10–14).

**Substrate scope.** Under the optimal conditions, various glycinal $\alpha$-keto amides containing alkyl (for 3b–e), aromatic (for 3a and 3f–i), or heteroatomic alkyl (for 3j–k) groups were all smoothly transaminated to give the corresponding N-Boc-protected glycinal dipeptides 3a–k in 70–94% yields with up to 98% ee (Fig. 4). Chiral glycinal $\alpha$-keto amide (for 3l) displayed excellent diastereoselectivity (98:2 dr). Transamination of $\alpha$-keto phenylbutanamides of chiral amino acid esters produced various N-Boc-protected glycinal dipeptides 3m–y in 56–93% yields with up to 99:1 diastereoselectivity. Peptidyl $\alpha$-keto amides were also effective for the asymmetric transamination, to form tripeptides 3z–ab and tetrapeptides 3ac–ad in 60–87% yields with excellent diastereoselectivities under very mild conditions. Various functional groups such as C-C double bond (for 3c, 3l and 3y), NH2-sensitive bromide (for 3j), silyl group (for 3k), OH group of Tyr (for 3s), NH group of Trp (for 3t), amide CONH2 of Asn (for 3v), Boc-protected Lys residue (for 3w), Boc-protected guanidine (for 3x), and basic NH2 group of Lys (for 3ab) were all well tolerated by the transamination likely due to the mild reaction conditions.

In order to investigate the impacts of catalyst and substrates on diastereomeric induction, several representative $\alpha$-keto amides (for 3m–n, 3r, 3v–y, and 3aa–ab) were examined respectively using (S)-
**Fig. 3 Investigation of reaction parameters.** TFEA = 2,2,2-trifluoroethanol. Reaction conditions: 2a (0.10 mmol), 4 (0.11 mmol), HOAc (0.40 mmol), base (0.20 mmol) in solvent (0.48 mL) and H$_2$O (0.12 mL) at 20 °C for 48 h unless otherwise stated. The reaction mixtures were then treated with di-tert-butyl dicarbonate (0.30 mmol) at rt for 3 h. Isolated yields based on α-keto amide 2a. The ee values were determined by HPLC analysis. Reaction time was 72 h.

1b (5 mol%), (R)-1b (5 mol%), and achiral pyridoxamine 7 (20 mol %) as the catalyst. The corresponding peptides were formed with $S$ configurations of the newly generated chiral centers from catalyst (R)-1b and $R$ configurations from (S)-1b. The chiral pyridoxamine catalyst dominated the stereoselectivity, while the chiral groups on the amino acid residues of the α-keto amides threw little influence on the diastereomeric induction probably due to being far away from the reaction centers as well as the flexibility of the skeletons of the α-keto amides. No matter which configuration of the catalyst 1b was applied, excellent diastereoselectivities were always obtained, even for α-keto amides (for 3n and 3aa) with a nearby bulky chiral amino acid residue and for those that displayed obvious substrate-induction on diastereoselectivity in 7-catalyzed non-asymmetric transamination (5:95 dr for 3r and 19:81 dr for 3x). For α-keto amide 2y bearing two nearby chiral centers, a pair of diastereomers ($R,R,S$)-3y and ($R,S,S$)-3y were respectively obtained in good yields with high enantiopurities by using (S)-1b and (R)-1b as the catalyst. The absolute configurations of the newly generated chiral centers of peptides 3 were assigned by analogy, based on the X-ray analysis of 3d, 3m, and 3r (also see Supplementary Figs. 1–3 in SI).

**Synthetic applications.** Divergent extending an additional amino acid unit from a central peptide is of great interest for peptide drug screening and bioactivity studies. The synthesis would be difficult when the extended unit is a commercially unavailable unnatural amino acid. The transamination process provides an efficient strategy for the amino acid extending. For example, starting from the benzyl ester of protease inhibitor Ubenimex (8)\textsuperscript{65}, condensation with α-keto acids and subsequent asymmetric transamination afforded a variety of enantiopure peptides 3ae-ai with one more amino acid residue extended (Fig. 5a).
Transamination of α-keto amides of chiral amino acid esters\(^a,b\)

\[
\begin{align*}
\text{MeO} & \quad \text{H} & \quad R & \quad \text{NHBoc} \\
(\text{S},\text{S},\text{R})-3a & 1b & 5 \text{ mol\%}) & \quad \text{(R)}-1b: 3a, 80\%, 97:3 \text{ dr} \\
(\text{S},\text{S},\text{R})-3a & 1b & 5 \text{ mol\%}) & \quad \text{R-S,R-S} & 3a, 78\%, 96\% \text{ ee} \\
(\text{S},\text{S},\text{R})-3a & 1b & 5 \text{ mol\%}) & \quad \text{R-S,S,R-S} & 3a, 57\%, 98:2 \text{ dr} \\
(\text{S},\text{S},\text{R})-3a & 1b & 5 \text{ mol\%}) & \quad \text{R-S,S,R-S} & 3a, 48\%, 44:56 \text{ dr}
\end{align*}
\]

**Fig. 4** Asymmetric biomimetic transamination of α-keto amides. TBDPS = tert-butylidiphenylylsilyl. \(^a\)Reaction conditions: 2 (0.10 mmol), 4 (0.11 mmol), 1b (0.0050 mmol), HOAc (0.40 mmol), Na$_2$HPO$_4$ or KOAc (0.20 mmol) in CF$_3$CH$_2$OH or MeOH (0.48 mL) and H$_2$O (0.12 mL) for 48 or 72 h unless otherwise stated (See SI). For 3m-y, the reactions were carried out in a double scale with 7 (0.040 mmol, 20 mol %) at 50 °C for 72 h.

unprotected OH group remained untouched during the condensation and transamination.

Based on the “condensation-transamination” process, a new strategy for the synthesis of peptides also can be developed. As illustrated in Fig. 5b, the methyl ester of DPP-IV inhibitor Diprotin A (10\(^b\)) underwent condensation with α-keto acid 9a and subsequent asymmetric transamination, forming tetrapeptide 3ad with excellent diastereoselectivity. Repeating the reaction sequence two more times afforded hexapeptide 3ak with high enantiopurity. The chirality of the extended amino acid residues was established along with the transamination process. The protocol is especially attractive for the synthesis of peptides made

\[\text{transamination of (S,R)-3a} \quad \text{(R)}-1b: 3a, 72\%, 2:98 \text{ dr} \]

\[\text{transamination of (S,R)-3b} \quad \text{(R)}-1b: 3b, 80\%, 97:3 \text{ dr} \]

\[\text{transamination of (S,R)-3c} \quad \text{(R)}-1b: 3c, 80\%, 97:3 \text{ dr} \]

\[\text{transamination of (S,R)-3d} \quad \text{(R)}-1b: 3d, 80\%, 97:3 \text{ dr} \]

\[\text{transamination of (S,R)-3e} \quad \text{(R)}-1b: 3e, 80\%, 97:3 \text{ dr} \]

\[\text{transamination of (S,R)-3f} \quad \text{(R)}-1b: 3f, 80\%, 97:3 \text{ dr} \]
of unnatural amino acids, since it doesn’t need great efforts to make NH₂-protected chiral unnatural amino acids before the amide bond formation.

**Reaction mechanism.** A plausible mechanism was proposed for the transamination (Fig. 6a). Pyridoxamine 1b condenses with α-keto amide 2 to form ketimine 11, which undergoes asymmetric 1,3-proton shift to aldimine 13 under the assistance of the amine side arm. Hydrolysis of aldimine 13 releases peptide 3 and generates the pyridoxal, which is in situ converted into iminium via intramolecular condensation. The iminium then undergoes decarboxylative transamination with the amine source diphenylglycine (4) back to pyridoxamine catalyst 1b, completing a catalytic cycle.

As expected, N-quatertization of the pyridine ring of the chiral pyridoxamines resulted in higher catalytic activity and better enantioselectivity for the asymmetric transamination (Fig. 6b, 1b vs 1g). The stronger electron-withdrawing property makes the benzyl C-H of ketimine 11 more acidic and also stabilizes the corresponding delocalized carbanion 12 better, thus favoring the 1,3-proton shift and accelerating the transamination process. The control experiment confirmed the amazing effect of the amine side arm again (Fig. 6b, 1b vs 1f). Introducing an acetyl group onto the nitrogen to eliminate the basicity of the amine on the side arm led to marked decreases in activity and enantioselectivity. The amine side arm not only promotes the 1,3-proton shift by acting as an intramolecular base to deprotonate the corresponding delocalized carbanion 12 but also helps to orient the α-keto amide by hydrogen bonding with the carbonyl oxygen of the amide group (Fig. 6c), resulting in improved activity and stereoselectivity.

Protonation of the delocalized carbanion 12 occurs at a position of the amide group from the up side of the pyridine ring away from the amine side arm, to form the newly generated chiral center with S configuration from catalyst (R)-1b.
Discussion

In summary, based on the concept of multiple imitation of transaminases, we have developed N-quaternized axially chiral pyridoxamines containing an amine side arm. With pyridoxamine 1b as the catalyst, challenging substrates α-keto amides were successfully transaminated to peptides in good yields with excellent enantio- and diastereoselectivities. The catalyst dominated the diastereoselective control for the transamination of chiral α-keto amides. Thus, a pair of diastereomeric peptides could be respectively obtained with high enantiopurities by...
switching the configuration of the pyridoxamine catalyst. The strong electron-withdrawing property of the N-quaternized pyridine ring together with the cooperative catalysis of the amine side arm account for the increased catalytic activity and selectivity of the pyridoxamine 1b in the transamination. The reaction can provide an efficient strategy for divergent and successive extension of peptides via condensation-transamination reaction sequence, which is especially attractive for the synthesis of peptides made of unnatural amino acids.

Methods

General procedure for the asymmetric biomimetic transamination Reaction (Fig. 4). A mixture of a α-keto amide 2 (0.10 mmol), chiral pyridoxamine 1b (0.0050 mmol), 2,2-diphenylglycine 4 (0.11 mmol), HAc (0.40 mmol), Na2HPO4 or KOAc (0.20 mmol), CF3CH2OH or MeOH (0.48 mL), and H2O (0.12 mL) was stirred at 16-25 °C for the specified time. For glycinyl α-keto amides (for 3a-I) and α-keto phenylbutanamides of amino acid esters (for 3m-y), the crude reaction mixtures were treated with di-tert-butyl dicarbonate (0.3 mmol) at room temperature for 3 h after the transamination was completed, then concentrated via rotary evaporator to remove most of the solvent and isolated by column chromatography on silica gel with a mixed solvent of dichloromethane, methanol and ammonia solution in ethanol (2.9 M) as the eluant to give the transamination products tripeptides 3a-aa and tetrapeptides 3ab-ad without NH3–protection. The ee and dr values of 3a-ac were determined by HPLC analysis.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information file, or from the corresponding author upon reasonable request. For the experimental procedures, characterization data, and NMR spectra along with HPLC chromatograms, see Supplementary Information. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers of CCDC 2036531 (3d), CCDC 2036532 (the cyclized derivative of 3m), and CCDC 2036529 (3r). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

Received: 15 December 2020; Accepted: 11 August 2021; Published online: 30 August 2021

References

1. Henninot, A., Collins, J. C. & Nuss, J. M. The current state of peptide drug discovery: back to the future? J. Med. Chem. 61, 1382–1414 (2018).
2. Lau, J. L. & Dunn, M. K. Therapeutic peptides: historical perspectives, current
3. Vlieghe, P., Lisowski, V., Martinez, J. & Khrestchatisky, M. Synthetic
4. Piliero, P. J. Atazanavir: A Novel HIV-1 Protease Inhibitor. Acc. Chem. Res. 28, 146–153 (1995).
5. Zimmerman, S. C. & Breslow, R. Asymmetric synthesis of amino acids by pyridoxamine enzyme analogs utilizing general base-acid catalysis. J. Am. Chem. Soc. 106, 1490–1491 (1984).
6. Wei, S., Wang, J., Venhuizen, S., Skouta, R. & Breslow, R. Dendrimers in solution can have their remote catalytic groups folded back into the core: enantioselective transaminations by dendritic enzyme mimics-II. Bioorg. Med. Chem. Lett. 19, 5543–5546 (2009).
7. Humphrey, J. M. & Chamberlin, A. R. Chemical synthesis of natural product peptides: coupling methods for the incorporation of noncoded amino acids into peptides. Chem. Rev. 97, 2243–2266 (1997).
8. El-Faham, A. & Albericio, F. Peptide coupling reagents, more than a letter soup. Chem. Rev. 111, 6557–6602 (2011).
9. Taylor, P. P., Pantalone, D. P., Senkpell, R. F. & Fotheringham, I. G. Novel biosynthetic approaches to the production of unnatural amino acids using transaminases. Trends Biotechnol. 16, 412–418 (1998).
10. Fuchs, M., Farnberger, J. E. & Krottil, W. The industrial age of biocatalytic transamination. Eur. J. Org. Chem. 2015, 6965–6982 (2015).
11. Metzler, D. E., Ikawa, M. & Snell, E. E. A general mechanism for vitamin B6–catalyzed reactions. J. Am. Chem. Soc. 76, 648–652 (1954).
12. Aylng, J. & Snell, E. E. Mechanism of action of pyridoxine pyruvate transaminase. Biochemistry 7, 1616–1625 (1968).
13. Liao, R.-Z., Ding, W.-J., Yu, J.-G., Fang, W.-H. & Liu, R.-Z. Theoretical studies on pyridoxyl 5’-phosphate-dependent transamination of α-amino acids. J. Comput. Chem. 29, 1919–1929 (2008).
14. Breslow, R. Biomimetic chemistry: bio as an inspiration. J. Biol. Chem. 284, 1337–1342 (2009).
15. Breslow, R. Biomimetic chemistry and artificial enzymes: catalysis by design. Acc. Chem. Res. 28, 146–153 (1995).
16. Xie, Y., Pan, H., Liu, M., Xiao, X. & Shi, Y. Progress in asymmetric biomimetic transamination of carbonyl compounds. Chem. Soc. Rev. 44, 1740–1748 (2015).
17. Chen, J., Liu, Y. E., Gong, X., Shi, L. & Zhao, B. Biomimetic chiral pyridoxal and pyridoxamine catalysts. Chin. J. Chem. 37, 103–112 (2019).
18. Kuzuhara, H., Komatsu, T. & Emoto, S. Synthesis of a chiral pyridoxamine analog and nonenzymatic stereoselective transamination. Tetrahedron Lett. 19, 3563–3566 (1978).
19. Breslow, R., Hammond, M. & Lauer, M. Selective transamination and optical induction by a β-cyclodextrin-pyridoxamine artificial enzyme. J. Am. Chem. Soc. 102, 421–422 (1980).
20. Zimmerman, S. C. & Breslow, R. Asymmetric synthesis of amino acids by pyridoxamine enzyme analogs utilizing general base-acid catalysis. J. Am. Chem. Soc. 106, 1490–1491 (1984).
21. Liew, Y. E. et al. Enzyme-inspired axially chiral pyridoxamines armed with a cooperative lateral amine chain for enantioselective biomimetic transamination. J. Am. Chem. Soc. 138, 10730–10733 (2016).
22. Bernauer, K., Deschenaux, R. & Taura, T. Stereoselectivity in reactions of metal complexes VII. Asymmetric synthesis of amino acids by metal ion-promoted transamination. Helv. Chim. Acta 66, 2049–2058 (1983).
23. Soloshonok, V. A., Kirilenko, A. G., Galushko, S. V. & Kukhar, V. P. Catalytic asymmetric imine isomerisation in the enantioselective synthesis of chiral amines from prochiral ketones. Tetrahedron Lett. 36, 3917–3920 (1995).
24. Holmencrantz, A. & Berg, U. New approach to biomimetic transamination using bifunctional [1,3]-proton transfer catalysis in thioxanthodine dioxide imines. J. Org. Chem. 67, 3585–3594 (2002).
25. Knudsen, K. R., Bachmann, S. & Jergensen, K. A. Catalytic enantioselective transamination of α-keto esters: an organic approach to enzymatic reactions. Chem. Commun. 20, 2602–2603 (2003).
26. Xiao, X., Xie, Y., Su, C., Liu, M. & Shi, Y. Organocatalytic asymmetric biomimetic transamination: from α-keto esters to optically active α-amino acid derivatives. J. Am. Chem. Soc. 133, 12914–12917 (2011).
27. Wu, Y. & Deng, L. Asymmetric synthesis of trifluoromethylated amines via catalytic enantioselective isomerization of imines. J. Am. Chem. Soc. 134, 14334–14337 (2012).
28. Xie, Y., Pan, H., Xiao, X., Li, S. & Shi, Y. Organocatalytic asymmetric biomimetic transamination of aromatic ketone to optically active amine. Org. Biomol. Chem. 10, 8960–8962 (2012).
29. Zhou, X., Wu, Y. & Deng, L. Cinchonine betaines as efficient catalysts for asymmetric proton transfer catalysis: the development of a practical enantioselective isomerization of trifluoromethyl imines. J. Am. Chem. Soc. 138, 12297–12302 (2016).
30. Kang, Q.-K., Selvakumar, S. & Maruoka, K. Asymmetric synthesis of α-amino acids by organocatalytic biomimetic transamination. Org. Lett. 21, 2294–2297 (2019).
31. Herbst, R. M. & Shenmin, D. The synthesis of peptides by transamination. J. Biol. Chem. 147, 541–547 (1943).
38. Lee, S. H., Kyung, H., Yokota, R., Goto, T. & Oe, T. N-terminal α-ketamide peptides: formation and transamination. *Chem. Res. Toxicol.* 27, 637–648 (2014).

39. Cennamo, C., Carafoli, B. & Bonetti, E. P. Non-enzymatic transamination between peptides and pyridoxal. Isolation of the 2,4-dinitrophenylhydrazones of some ketopeptides. *J. Am. Chem. Soc.* 78, 3532–3537 (1956).

40. Dixon, H. Transamination of peptides. *Biochem. J.* 92, 661–666 (1964).

41. Papapoulos, A., Rademam, J. & Moldal, M. pyridoxal peptides: a general approach to reactive resin-bound intermediates in the synthesis of peptide isosteres for peptoid inhibitor screening on solid support. *J. Am. Chem. Soc.* 123, 2176–2181 (2001).

42. Gilmore, J. M., Scheck, R. A., Esser-Kahn, A. P., Joshi, N. S. & Francis, M. B. Optimization and expansion of a site-selective N-methylpyridinium-4-carboxaldehyde-mediated transamination reaction for bacterially expressed proteins. *J. Am. Chem. Soc.* 137, 1123–1129 (2015).

43. Soda, K., Yoshimura, T. & Esaki, N. Stereospecificity for the hydrogen transfer and molecular evolution of pyridoxine enzymes. *Biosci. Biotechnol. Biochem.* 60, 181–196 (1996).

44. Soda, K., Yoshimura, T. & Esaki, N. Stereospecificity for the hydrogen transfer of pyridoxal enzymes. *Chem. Rec.* 1, 373–384 (2001).

45. Kirsch, J. F. et al. Mechanism of action of aspartate aminotransferase proposed on the basis of its spatial structure. *J. Mol. Biol.* 174, 497–525 (1984).

46. Kochhar, S., Finlayson, W. L., Kirsch, J. F. & Christen, P. The stereospecific labilization of the C-4′ pro-S hydrogen of pyridoxamine 5′-phosphate is abolished in (Lys258→fi)-aspartate aminotransferase. *J. Biol. Chem.* 262, 11446–11448 (1987).

47. Malashkevich, V. N. et al. Structural basis for the catalytic activity of aspartate aminotransferase K258H lacking the pyridoxal 5′-phosphate-binding lysine residue. *Biochemistry* 34, 405–414 (1995).

48. Aandroer, M. et al. Towards a detailed description of pyridoxine tautomeric species. *N. J. Chem.* 36, 1751–1761 (2012).

49. Gansow, O. A. & Holm, R. H. Aqueous solution equilibria of pyridoxamine, pyridoxal, 3-hydroxypyridine-4-aldehyde, and 3-hydroxypyridine-2-aldehyde as studied by proton resonance. *Tetrahedron* 24, 4477–4487 (1968).

50. Limbach, H.-H. et al. Critical hydrogen bonds and protonation states of pyridoxal 5′-phosphate revealed by NMR. *Biochim. Biophys. Acta* 1814, 1426–1437 (2011).

51. Yano, T., Kuramitsu, S., Toda, S., Morino, Y. & Kagamiyama, H. Role of Asp222 in the catalytic mechanism of Escherichia coli aspartate aminotransferase: the amino acid residue which enhances the function of the enzyme-bound coenzyme pyridoxal 5′-phosphate. *Biochemistry* 31, 5878–5887 (1992).

52. Sharif, S. et al. NMR localization of protons in critical enzyme hydroxyl bonds. *J. Am. Chem. Soc.* 129, 9538–9539 (2007).

53. Grisswold, W. B. & Toney, M. D. Role of the pyridine nitrogen in pyridoxal 5′-phosphate catalysis: activity of three classes of plp enzymes reconstituted with deazapyridoxal 5′-phosphate. *J. Am. Chem. Soc.* 133, 14823–14830 (2011).

54. Crugge, J., Rios, A., Riveiros, E. & Richard, J. P. Substituent effects on electrophilic catalysis by the carbonyl group: anatomy of the rate acceleration for PLP-catalyzed depolymerization of glycine. *J. Am. Chem. Soc.* 133, 3173–3183 (2011).

55. Crugge, J., Rios, A., Ameyes, T. L. & Richard, J. P. Carbon acidity of the α-pyridinium carbon of a pyridoxine analog. *Org. Biomol. Chem.* 3, 2145–2149 (2005).

56. Bucklay, T. E. & Rapoport, H. Mild and simple biomimetic conversion of α-amino to α-keto compounds. *J. Am. Chem. Soc.* 104, 4466–4468 (1982).

57. Chen, J. et al. Carbonyl catalysis enables a biomimetic asymmetric Mannich reaction. *Science* 360, 1438–1442 (2018).

58. Cheng, A. et al. Efficient Asymmetric Biomimetic Aldol Reaction of Glicynates and Tri fluoromethyl Ketones by Carbonyl Catalysis. *Angew. Chem. Int. Ed.* https://doi.org/10.1002/anie.202014031 (2021).

59. Ma, J. et al. Enantioselective synthesis of pyrogulic acid esters from glycinate via carbonyl catalysis. *Angew. Chem. Int. Ed.* 60, 10588–10592 (2021).

60. Liu, L., Zhou, W., Chrumpa, J. & Breslow, R. Transamination reactions with multiple turnovers catalyzed by hydrophobic pyridoxine cofactors in the presence of polyethyleneimine polymers. *J. Am. Chem. Soc.* 126, 8136–8137 (2004).

61. Yamazaki, Y. et al. Acid catalyzed monodehydro-2,5-diketopiperazine formation from N-α-ketoacyl amino acid amides. *Tetrahedron* 65, 3868–3869 (2009).

62. Yoneda, J. et al. Inhibition of tumor invasion and extracellular matrix degradation by ubenimex (bestatin). *Clin. Exp. Metastasis* 10, 49–59 (1992).

63. Juillet-Jeanerent, L. Dipetidyl peptidase IV and its inhibitors: therapeutics for type 2 diabetes and what else? *J. Med. Chem.* 57, 2197–2212 (2014).

64. Gonzalez, J., Rios, A., Riveiros, E., Amyes, T. L. & Richard, J. P. Glycine catalyzes the effect of formation of iminio ions to simple ketones on α-amino carbon acidity and a comparison with pyridoxal iminium ions. *J. Am. Chem. Soc.* 130, 2041–2050 (2008).

65. Angew. Chem. Int. Ed. 130, 2041–2050 (2008).

66. Chen, W.-W. & Zhao, B. Decarboxylative umpolung synthesis of amines from carbonyl compounds. *Synlett* 31, 1543–1550 (2020).

**Acknowledgements**

We are grateful for the generous financial support from the National Natural Science Foundation of China (21672148, 21871181), the Shanghai Municipal Education Commission (2019-01-07-00-02-E00029), the Shanghai Municipal Committee of Science and Technology (18ZR1447600, 20CR1468000), “111” Innovation and Talent Recruitment Program, the Ministry of Science and Technology of China (21871181), and the Shanghai Engineering Research Center of Green Energy Chemical Engineering (18DZ2254200).

**Author contributions**

B.Z. conceived and directed the project and wrote the paper. W.C and X.Q. conducted most of the experiments including the synthesis of the chiral pyridoxamine catalysts and the development of the asymmetric biomimetic transamination reaction. H.Z. synthesized some pyridoxamine intermediates and several α-keto amides for the transamination. B.L. performed some experiments for the catalyst development. J.G. and L.Z. synthesized several α-keto amides for the transamination. W.C. revised the manuscript and the Supplementary Information.

**Competing interests**

The authors declare no competing interests.

**Additional information**

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41467-021-25449-y.

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