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Chiral Pyridoxal-Catalyzed Asymmetric Biomimetic Transamination of α-Keto Acids

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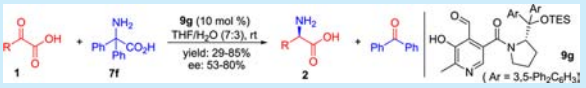
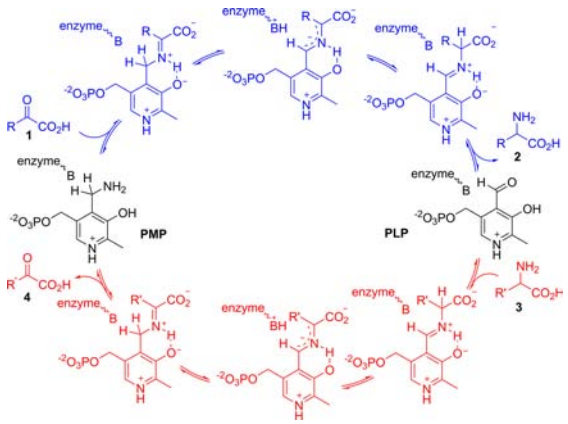
Supporting Information

ABSTRACT: A series of chiral pyridoxals **8** and **9** have been developed from commercially available pyridoxine and (*S*)-α,α-diarylprolinols. The pyridoxals exhibited good catalytic activity in an asymmetric transamination of α-keto acids with 2,2-diphenylglycine (**7f**) as the amine source to give various α-amino acids in 29−85% yields with 53−80% ee's. The current asymmetric transamination has successfully mimicked a complete biological transamination process characterized by two half-transaminations, a small chiral pyridoxal molecule acting as the catalyst, and enantioselective control.



Biological transamination of α-keto acids to α-amino acids is one of the most important biological processes, and it is promoted by transaminase with pyridoxal 5′-phosphate (PLP) or pyridoxamine 5′-phosphate (PMP) acting as the catalytic center (Scheme 1).[1] A complete biological transamination process includes two half-transaminations. One of the half-transaminations involves pyridoxamine 5′-phosphate (PMP) transferring its NH_2 group to α-keto acid **1** via Schiff base formation, 1,3-hydrogen shift, and subsequent hydrolysis to give the α-amino acid **2** and pyridoxal 5′-phosphate (PLP). The pyridoxal 5′-phosphate undergoes a reverse process, i.e. another half-transamination with α-amino acid **3** as the amine source, to regenerate pyridoxamine 5′-phosphate, completing the catalytic cycle. Imitation of this biological process is of great significance to biochemistry[1−3] and is also highly attractive for the synthesis of optically active α-amino acids.[2,4−9]

Scheme 1. Biological Transamination of α-Keto Acids



Inspired by biological transamination, great efforts have been made toward the pyridoxal/pyridoxamine-based biomimetic asymmetric transamination of α-keto acids since the 1970s.[4−8] The studies include asymmetric transamination with stoichiometric chiral pyridoxamine analogues as the amine sources (Scheme 2a),[4] with stoichiometric pyridoxamine or its achiral derivatives catalyzed by chiral Lewis acids[5] or induced by chiral polymers[4o,6] (Scheme 2b), and that catalyzed by a supramolecular catalyst[7] or semisynthetic transaminase[8] (Scheme 2c). The asymmetric transaminations using pyridoxamine and its analogues as amine sources were the most studied (Scheme 2a and b),[4−6] as they mimicked the half-transamination process that started from keto acid **1** and PMP to amino acid **2** and PLP, as shown in blue in Scheme 1. The supramolecular catalyst developed by Murakami is a bilayer membrane self-assembled from peptide lipid **5**, hydrophobic pyridoxal **6**, and a Cu(II) complex (Scheme 2c).[7] The semisynthetic transaminase was made by covalently conjugating a pyridoxamine moiety to a fatty acid binding protein.[8] Both of the catalytic systems displayed turnover behavior and good enantioselectivity in the asymmetric transamination of α-keto acids; however, their accurate chemical structures are difficult to be defined, and it is not easy to make a targeted catalyst modification. Catalytic asymmetric transamination of α-keto acids biomimicking two half-transamination processes using small chiral pyridoxal/pyridoxamine molecules as the catalyst has not yet emerged to the best of our knowledge, remaining a significant challenge in organic chemistry. Herein, we developed a new class of chiral pyridoxals **8**−**9** containing α,α-diarylprolinol moieties and also realized **8**/**9**-catalyzed asymmetric biomimetic transamination of α-keto acids to α-amino acids (Scheme 2). Here, we report our preliminary results on the subject.

The studies commenced with the synthesis of chiral pyridoxals **8**−**9** using the commercially available pyridoxine hydrochloride **10** as the starting material (Scheme 3). The 3-hydroxy and 4-

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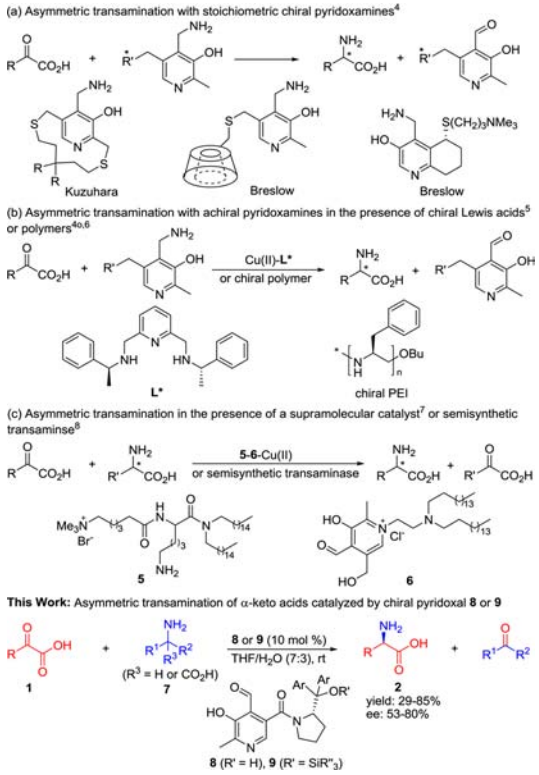
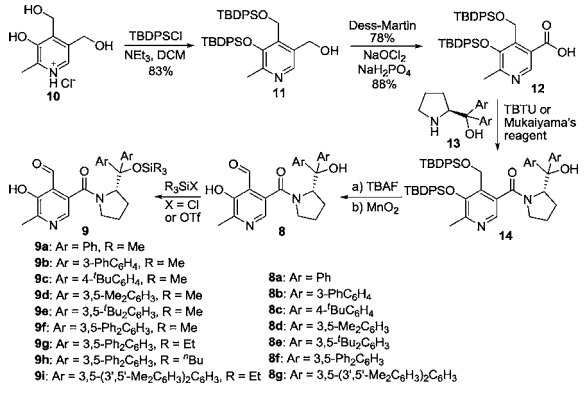
Scheme 2. Pyridoxal/Pyridoxamine-Based Biomimetic Asymmetric Transamination of α-Keto Acids



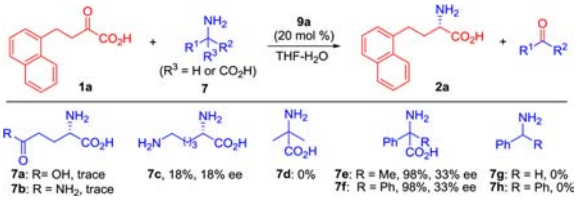
Scheme 3. Synthesis of Chiral Pyridoxals 8 and 9



pyridinemethoxy of pyridoxine **10** were selectively protected with a *tert*-butyldiphenylsilyl group (TBDPS) to give compound **11** in 83% yield, which was further converted into acid **12** in good yield via Dess-Martin oxidation and Pinnick oxidation. Condensation of compound **12** with(*S*)-α,α-diarylprolinol **13** prepared from L-proline, followed by removal of the silyl groups with tetrabutylammonium fluoride (TBAF) and oxidation with MnO_2, gave the chiral pyridoxals **8**. More bulky chiral pyridoxals **9** were also obtained by protecting the hydroxyl group of **8** with silyl chloride or triflate. All of the pyridoxals including **8a−g** and **9a−i** are yellow solids and can be stored in the freezer for several months without obvious decomposition.

With chiral pyridoxals **8−9** in hand, we then tried to realize **8**/**9**-catalyzed asymmetric transamination of α-keto acids. In the studies, 4-(naphthalen-1-yl)-2-oxobutanoic acid (**1a**) was chosen as the model substrate due to its strong fluorescence intensity favoring TLC analysis (Table 1). Various amine sources

Table 1. Screening of Amine Sources for 9a-Catalyzed Asymmetric Transamination of α-Keto Acids[a]

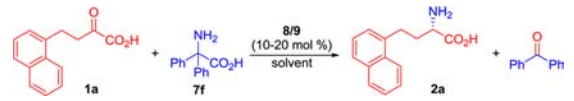


[a]All the reactions were carried out with **1a** (0.10 mmol), amine source **7** (0.12 mmol), **9a** (0.020 mmol) in THF−H_2O (7:3, 1.0 mL) at rt for 3 d unless otherwise stated. For **7a−c**, MeOH−H_2O (9:1, 1.0 mL) was used. Isolated yields were based on **1a**. The ee's were determined by chiral HPLC analysis of the methyl ester of **2a**.

including amino acids **7a−f** and benzylamines **7g−h** were examined (Table 1). L-Lysine (**7c**) showed low reactivity for the transamination, while methylphenylglycine **7e** and diphenylglycine **7f** both gave good results in terms of activity and enantioselectivity, which underwent oxidative decarboxylation in the transamination as the sacrificial amine source.[10,11] Diphenylglycine **7f** was chosen as the amine source in the following studies due to its ready availability.

The impact of the catalyst and reaction conditions on the transamination were also investigated [Table 2 and Supporting Information (SI)]. Silyl-protected chiral pyridoxals **9** are more enantioselective than the corresponding unprotected ones **8** (Table 2, entry 2 vs 1; also see SI). Pyridoxal **9g** displayed the highest enantioselectivity (Table 2, entry 5). Water is crucial for the transformation (Table 2, entry 8 vs entries 1−7), probably because it promotes hydrolysis of various imines (Scheme 1). A

Table 2. Optimization of Reaction Conditions[a]



entry	cat.	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	**8b**	THF−H_2O (7:3)	18	63	40
2	**9b**	THF−H_2O (7:3)	18	71	50
3	**9e**	THF−H_2O (7:3)	18	42	55
4	**9f**	THF−H_2O (7:3)	48	48	65
5	**9g**	THF−H_2O (7:3)	16	64	80
6	**9h**	THF−H_2O (7:3)	16	48	77
7	**9i**	THF−H_2O (7:3)	16	41	77
8	**9g**	THF	18	trace	ND
9	**9g**	THF−H_2O (5:5)	16	66	78
10	**9g**	EtOH−H_2O (7:3)	18	22	50
11	**9g**	THF−H_2O (7:3)	15	53	64
12	**9g**	THF−H_2O (7:3)	15	65	78
13	**9g**	THF−H_2O (7:3)	18	54	51
14	**9g**	THF−H_2O (7:3)	72	37	79
15	**9g**	THF−H_2O (7:3)	72	85	79

[a]All the reactions were carried out with **1a** (0.10 mmol), 2,2-diphenylglycine **7f** (0.12 mmol), **8** or **9** (0.020 mmol) in solvent (1.0 mL) at rt unless otherwise stated. For entries 11−13, NEt_3 (0.050 mmol), HOAc (0.050 mmol), and $NH_4Al(SO_4)_2{\cdot}12H_2O$ (0.020 mmol) were respectively added. For entry 14, the reaction was carried out at 10 °C. For entry 15, **1a** (0.20 mmol), **7f** (0.22 mmol), **9g** (0.020 mmol), and THF−H_2O (7:3, 2.0 mL) were used. [b]Isolated yield based on **1a**. [c]Determined by chiral HPLC analysis of the corresponding methyl ester of **2a**.

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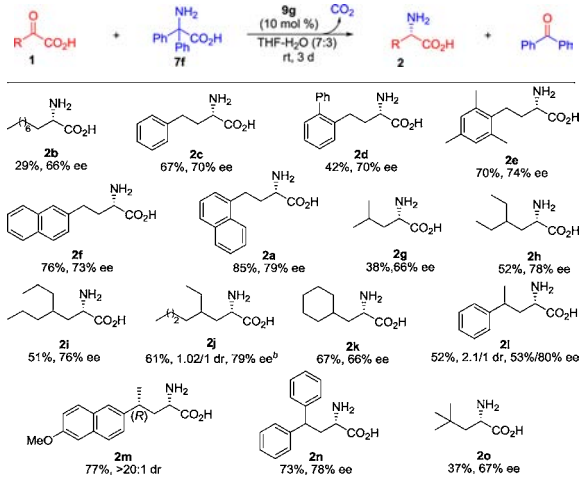
mixed system of THF and H_2O (7:3) was chosen as the solvent for the transamination (Table 2, entry 5). An additional additive such as NEt_3 and $NH_4Al_2(SO_4)_2$ led to a decrease of ee (Table 2, entries 11 and 13). A lower temperature disfavored the reaction in terms of activity (Table 2, entry 14 vs 5). When the catalyst loading was lowered to 10 mol %, good results were also obtained by running the reaction for 3 days (Table 2, entry 15).

Under the optimal conditions, the substrate scope was then examined. Various aliphatic linear (for **2b**), aromatic linear (for **2a**, **2c**−**f**), γ-monosubstituted (for **2g**−**n**), and γ,γ-disubstituted (for **2o**) α-keto acids were all smoothly transaminated with **7f** to give the corresponding α-amino acids in 29−85% yields with 53−80% ee's. Keto acids with sterically bulky side chains exhibited relatively higher enantioselectivity in the transamination (see **2a**, **2h**−**i**, and **2n**). Moderate diastereoselectivity was observed for 2-oxo-4-phenylpentanoic acid bearing a stereogenic center (for **21**). The minor diastereoisomer has a higher ee than the major one (80% vs 53% ee). An excellent dr value (>20:1) was obtained in the asymmetric transamination of chiral substrate (*S*)-4-(6-methoxynaphthalene-2-yl)-2-oxopentanic acid, suggesting good matching between the chiral center and the catalyst **9g** during chirality induction (Table 3, **2m**). β-Substituted keto acids such as 2-oxoisovaleric acid are ineffective for the transamination likely due to steric hindrance.

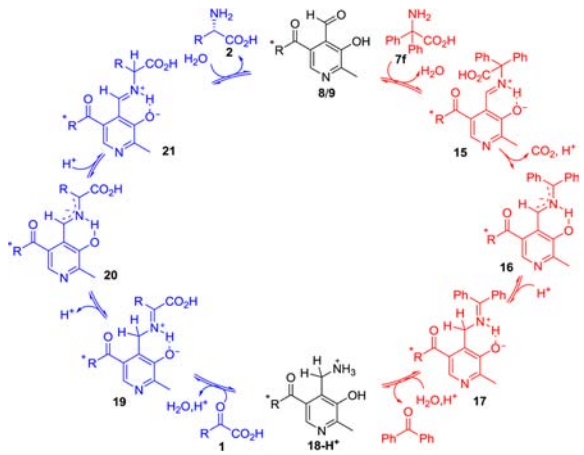
A plausible catalytic cycle was proposed for the transamination (Scheme 4). Pyridoxal **8** or **9** condenses with **7f** to form Schiff base **15**, followed by decarboxylation to generate a delocalized azaallylanion **16**.[10,11,13] The azaallylanion **16** is protonated at the pyridine-4-ylmethenyl carbon to give aldimine **17** which is further hydrolyzed and immediately protonated by α-keto acid **1**

Table 3. Substrate Screening for the Asymmetric Transamination of α-Keto Acids[a]



[a]All the reactions were carried out with **1** (0.20 mmol), **7f** (0.22 mmol), **9g** (0.020 mmol) in THF−H_2O (7:3, 2.0 mL) at rt for 3 d. Isolated yield based on **1**. The ee's were determined by chiral HPLC analysis after the α-amino acids were converted into the corresponding methyl ester for **2a** and amino-protected esters for **2b**−**l** and **2n**−**o**. The dr value of **2j** was determined by HPLC analysis after the amino acid was converted into its *N*-benzoyl methyl ester. The dr values of **2l** and **2m** were determined by ^1H NMR analysis in D_2O respectively containing 2 equiv of KOH and 20% (m/m) KOH. The absolute configurations of **2c**, **2g**, and **2k** were assigned as *S* by comparison of their optical rotations with the reported ones (ref 12). The absolute configurations of other amino acids were tentatively proposed by analog. [b]The average ee of the two diastereoisomers.

Scheme 4. A Proposed Mechanism for the Asymmetric Transamination of α-Keto Acids



to give chiral protonated pyridoxamine **18-H**$^+$ along with benzophenone, completing the first half-transamination. The pyridoxamine **18-H**$^+$ condenses with α-keto acid **1** to form ketimine **19**. Deprotonation of **19** at the 4-pyridinemethylene position and subsequent asymmetric protonation of the azaallylanion **20** at the α-C of the carboxyl group affords aldimine **21**. Hydrolysis of aldimine **21** gives chiral amino acid **2** and regenerates pyridoxal catalyst **8** or **9**, finishing a whole catalytic cycle of the transamination.

Control experiments (SI) showed that transamination of pyridoxal **8e** with **7f** could form chiral pyridoxamine **18e** smoothly and the reaction of the preprepared **18e** and α-keto acid **1a** gave α-amino acid **2a** in 82% yield and 41% ee, confirming the proposed pathway for the transamination. Pyridoxal **8e** was used in the studies because it does not contain a labile silyl group and also displayed enantioselectivity in the asymmetric transamination comparable to that for the best catalyst, **9g** (SI, Table S1, entry 9 vs 13). The ee of **2a** is somewhat lower than that obtained in the corresponding catalytic transamination (41% vs 68% ee) (Table S1, entry 9), probably due to partial racemization of **2a** by the stoichiometric pyridoxal **8e** generated in the noncatalytic transamination (SI).[14] In the catalytic version of the transamination, the regenerated pyridoxal **8e** should be immediately converted into the pyridoxamine and/or the related intermediates; thus, the racemization was suppressed.

NMR studies indicated that the resting state of the catalyst is the protonated pyridoxamine **18-H**$^+$ (SI). It has been reported that a Schiff base formed from pyridoxamine and α-keto acid is always in rapid equilibrium with its components in solution and the Schiff base formation constant usually is very low under acidic conditions.[15] Therefore, the following mechanism profile should be reasonable for the transamination: (a) the protonated pyridoxamine **18-H**$^+$, serving as the resting state of the catalyst, is in rapid equilibrium with α-keto acid **1** and the corresponding ketimine **19** (Scheme 4); (b) deprotonation of the imino C−H of ketimine **19** is the rate-determining step for the transamination.[15b,16] The solvent isotope effect may provide additional support for the presumption regarding the rate-determining step.[16b,17] Transamination was obviously faster in THF/H_2O than in THF/D_2O as judged by TLC analysis and the isolated yields (SI). The transamination in THF/D_2O was supposed to proceed via an imino-CH-deuterated **19**. The rate difference confirmed the above proposal that deprotonation of

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the imino C−H of **19** is the rate-determining step for the transamination.

In summary, we have developed a class of novel chiral pyridoxals **8**−**9** starting from pyridoxine and (*S*)-α,α-diarylprolinols, which displayed high catalytic activity and good enantioselectivity in the transamination of α-keto acids to give various optically active α-amino acids in 29−85% yields with 53−80% ee's under mild conditions. This work represents the first chiral-pyridoxal-catalyzed asymmetric biomimetic transamination of α-keto acids involving two half-transaminations and serves as an impressive example for the application of pyridoxals in asymmetric catalysis. Further studies on detailed mechanisms, developing more efficient catalysts, and expanding catalysis applications of chiral pyridoxals are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02895.

Procedures for synthesis of compounds **8**−**9** and transamination of α-keto acids, characterization data, and NMR spectra along with HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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