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Asymmetric Transamination of α-Keto Acids Catalyzed by Chiral Pyridoxamines

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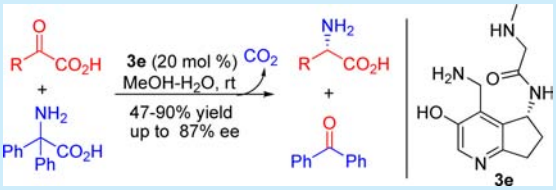
Supporting Information

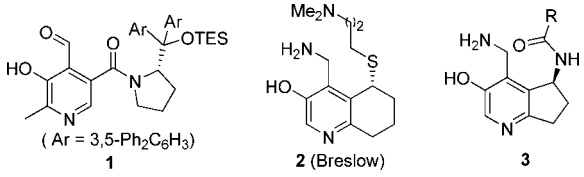
ABSTRACT: A new type of novel chiral pyridoxamines **3a–g** containing a side chain has been developed. The pyridoxamines displayed catalytic activity and promising enantioselectivity in biomimetic asymmetric transamination of α-keto acids, to give various α-amino acids in 47–90% yields with up to 87% ee's under very mild conditions. An interesting effect of the side chain on enantioselectivity was observed in the reaction.



Transamination of α-keto acids is one of the most important transformations in biological systems and provides various chiral amino acids to sustain the metabolism of lives.[1] Besides the biological significance, enzymatic transamination also has been broadly applied in industrial synthesis of pharmaceuticals and fine chemicals.[2,3] Imitation of the biological process, i.e. biomimetic asymmetric transamination, represents an intriguing method for the synthesis of optically active amino acids.[4,5] Great efforts have been contributed to this area including pyridoxal/pyridoxamine-based enantioselective transamination[6−11] and chiral bases or acids promoted/catalyzed asymmetric 1,3-proton transfer of imines.[12] Pyridoxal/pyridoxamine and their phosphates are the coenzymes of transaminases, serving as the catalytic center in enzymatic transamination.[1] In the absence of enzymes, pyridoxal/pyridoxamine and their analogues can promote or catalyze transamination of α-keto acids.[5,6] And the structure of the pyridoxal/pyridoxamine derivatives is remarkably influential regarding enantioselectivity and activity in the transamination. Therefore, searching for new chiral pyridoxal/pyridoxamine catalysts is significant and highly desirable for the development of the chemistry.[13,14]

Very recently, we reported a catalytic asymmetric transamination of α-keto acids with pyridoxal **1** bearing an (*S*)-α,α-diarylprolinol moiety as the catalyst (Scheme 1), to provide a series of α-amino acids in 29–85% yields with 53–80% ee's.[11] As a part of further studies on biomimetic asymmetric transamination, we have been focusing on developing new pyridoxal/pyridoxamine catalysts. In 1984, Breslow and his coworkers developed a novel chiral pyridoxamine analogue **2** tethered with a side amine arm.[6h,i] By using stoichiometric chiral pyridoxamine **2** as the amino source, asymmetric transamination of α-keto acids was realized with excellent enantioselectivity (up to 92% ee) in the presence of zinc acetate. Encouraged by this work, we designed and synthesized a new class of chiral pyridoxamines **3** with a rigid fused five-membered ring and a chiral side arm for catalytic asymmetric transamination. Herein, we report our results on the subject.

Scheme 1. Chiral Pyridoxals 1 and Pyridoxamines 2−3



The studies commenced with the synthesis of chiral pyridoxamines **3** (Scheme 2). By following a similar method to Breslow's,[6h] the pyridine skeleton was constructed via Diels–Alder reaction between diethyl maleate **4** and ethoxyoxazole **5**. The pyridine derivative **6** then underwent protection of the hydroxyl group with benzyl bromide, intramolecular Claisen condensation, and subsequent decarboxylation to give cyclopenta[*b*]pyridine-5-one **7** in good yield. Condensation of the cyclic ketone **7** with (*S*)-*tert*-butylsulfinamide, followed by reduction with $NaBH_4$, gave a pair of chromatographically separable diasteroisomers (*S*,*R*)-**8** and (*S*,*S*)-**8**. The structure and absolute configuration of compound (*S*,*R*)-**8** were confirmed by X-ray analysis (Figure 1). Enantiopure (*S*,*R*)-**8** was converted to hydroxyl amine **9** by reduction of the ester group with $LiAlH_4$ and subsequent deprotection with HCl (6 M). Condensation of **9** with a carboxylic acid gave compound **10** with a side amide arm, which was further converted into the desired chiral pyridoxamines **3** via reaction with diphenylphosphoryl azide (DPPA) and Pd/C-catalyzed hydrogenation. For compounds **3d–f** containing a NH side chain, *N*-Boc protected carboxylic acids were used in the condensation with primary amine **9**; thus, an additional step for the deprotection of the Boc group with an acid was employed in the synthesis of **3** from intermediates **10**.

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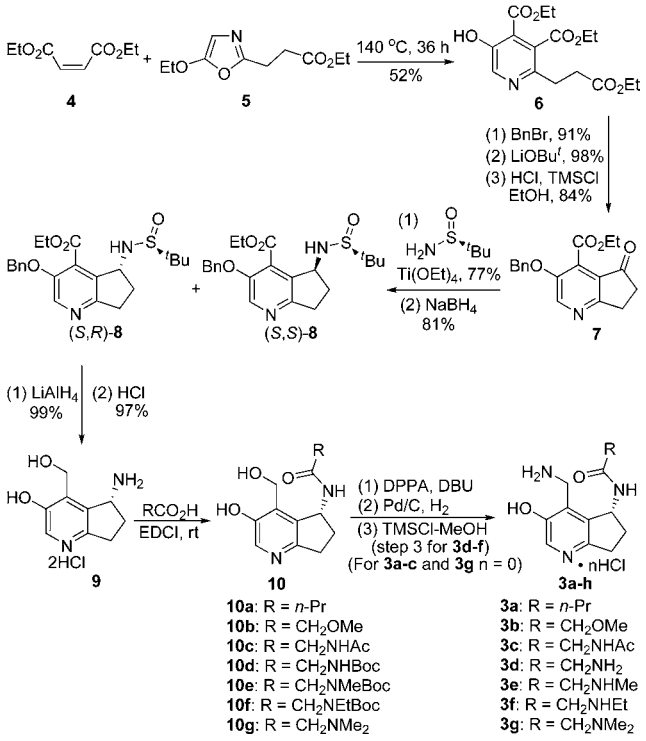
Scheme 2. Synthesis of Chiral Pyridoxamines 3



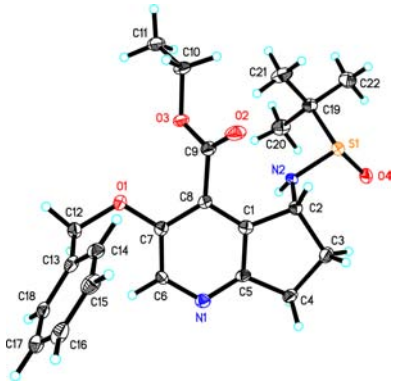


Figure 1. X-ray structure of compound (*S*,*R*)-**8**.

The chiral pyridoxamines **3a**−**g** were then examined in the asymmetric transamination of α-keto acid **11a** with 2,2-diphenylglycine (**12**) as the sacrificial amine source (Table 1).[15−17] All of the pyridoxamines exhibited catalytic activity for the transamination (Table 1, entries 1−7). Chiral pyridoxamines bearing an amine side chain such as **3d**−**g** are more enantioselective catalysts (Table 1, entries 4−7 vs 1−3). And pyridoxamine **3e** displayed the best performance in terms of enantioselectivity and activity in the transamination (Table 1, entry 5). Water has an obvious impact on the transamination (Table 1, entries 8−11). A mixed MeOH−H_2O (7:3) was chosen as the solvent (Table 1, entries 10 and 12−15). A buffer system such as Na_2HPO_4−citric acid buffer did not help to improve the activity and enantioselectivity for the transamination (Table 1, entries 16 and 17). A high temperature (30 °C) led to a decrease of enantioselectivity (Table 1, entry 18), while a low temperature (5 °C) resulted in a remarkable loss of activity (Table 1, entry 19). Lewis acid additives such as $NH_4Al(SO_4)_2$ and $Zn(OAc)_2$ led to an obvious negative effect on enantioselectivity and activity (Table 1, entries 21 and 22).

Table 1. Optimization of Reaction Conditions for the Asymmetric Transamination of α-Keto Acids[a]

entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	**3a**	MeOH−H_2O (9:1)	81	17
2	**3b**	MeOH−H_2O (9:1)	39	22
3	**3c**	MeOH−H_2O (9:1)	57	50
4	**3d**	MeOH−H_2O (9:1)	31	76
5	**3e**	MeOH−H_2O (9:1)	48	74
6	**3f**	MeOH−H_2O (9:1)	44	57
7	**3g**	MeOH−H_2O (9:1)	39	64
8	**3e**	MeOH	27	53
9	**3e**	MeOH−H_2O (8:2)	23	76
10	**3e**	MeOH−H_2O (7:3)	22	78
11	**3e**	MeOH−H_2O (6:4)	19	76
12	**3e**	THF−H_2O (7:3)	16	39
13	**3e**	EtOH/H_2O (7:3)	28	64
14	**3e**	DMF/H_2O (7:3)	40	54
15	**3e**	$CHCl_3$/H_2O (7:3)	trace	
16	**3e**	buffer (pH = 5.0)[d]	37	16
17	**3e**	buffer (pH = 7.4)[e]	39	66
18[f]	**3e**	MeOH−H_2O (7:3)	38	66
19[g]	**3e**	MeOH−H_2O (7:3)	35	80
20	**3e**	MeOH−H_2O (7:3)	76	70
21[h]	**3e**	MeOH−H_2O (7:3)	12	46
22[i]	**3e**	MeOH−H_2O (7:3)	31	36

[a]All the reactions were carried out with α-amino acid **11a** (0.10 mmol), 2,2-diphenylglycine **12** (0.10 mmol), catalyst **3** (0.010 mmol for entries 8−18 and 21−22, 0.020 mmol for entries 1−7 and 19−20) in solvent (1.0 mL) at room temperature for 3 d unless otherwise stated. The reaction time was 6 d for entries 19−20 and 2 d for entries 1−7. [b]Isolated yield based on **11a**. [c]Determined by chiral HPLC analysis of the corresponding methyl ester of the amino acid **13a**. [d]Na_2HPO_4 0.103 M, citric acid 0.0485 M. [e]Na_2HPO_4 0.182 M, citric acid 0.00915 M. [f]The reaction was carried out at 30 °C. [g]The reaction was carried out at 5 °C. [h]$NH_4Al(SO_4)_2$ (0.050 mmol) was added. [i]$Zn(OAc)_2$ (0.0010 mmol) was added.

Moderate enantioselectivity (70% ee) and a good yield (76%) could be obtained when the transamination was carried out with 20 mol % of **3e** as the catalyst at room temperature for 6 days (Table 1, entry 20). The reaction is heterogeneous at the outset owing to the low solubility of 2,2-diphenylglycine (**12**) in MeOH−H_2O (8:2). Compound **12** was gradually consumed as the reaction proceeded, and most of the white solid disappeared at the end of the reaction.

Under the established optimal conditions, the substrate scope was then examined for the catalytic asymmetric transamination (Scheme 3). Various aliphatic linear (Scheme 3, for **13b**−**f**), aromatic linear (Scheme 3, for **13a** and **13g**−**k**), and γ-substituted (Scheme 3, for **13l**−**n**) α-keto acids could be smoothly asymmetrically transaminated with 2,2-diphenylglycine (**12**) in the presence of 20 mol % of the catalyst **3e**, to give the corresponding optically active α-amino acids in 47−90% yields with 63−87% ee's. α-Keto acids with a bigger chain displayed a relatively higher enantioselectivity in the reaction (Scheme 3, **13d**−**e** vs **13b** and **13n** vs **13l**). 2-Oxopentanedioic acid (Scheme 3, for **13o**) was also transaminated in an 82% yield under the conditions. The additional carboxylic group

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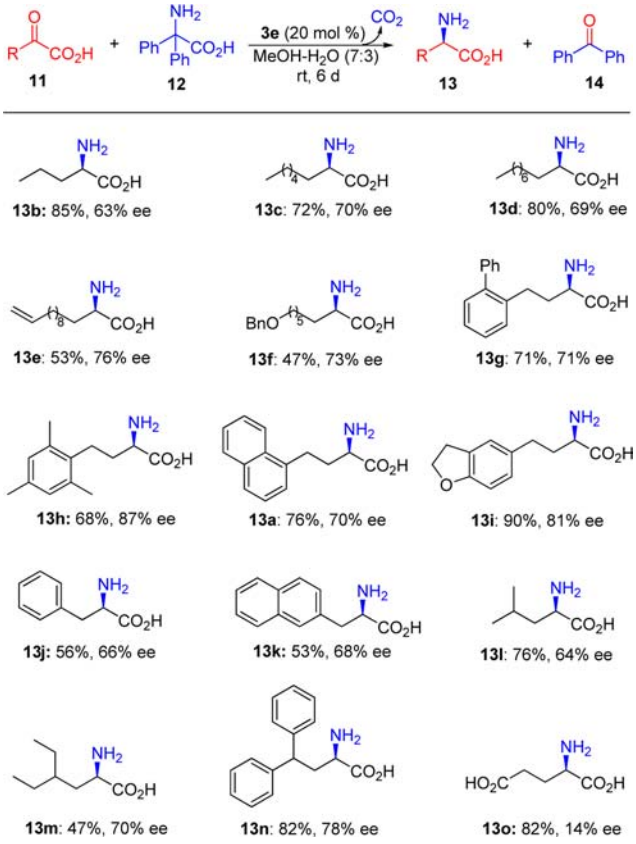
Scheme 3. Substrate Screening for the Asymmetric Transamination of α-Keto Acids[a]



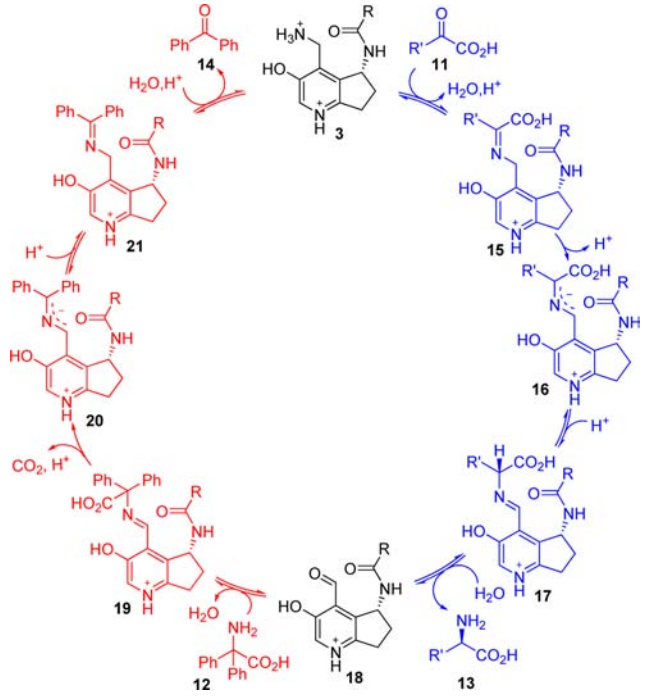
[a]All reactions were carried out with α-keto acids **11** (0.10 mmol), 2,2-diphenylglycine **12** (0.10 mmol), catalyst **3e** (0.020 mmol) in MeOH−H_2O (7:3, 1.0 mL) at room temperature for 6 d unless otherwise stated. For **13b−c**, **13j**, **13l−m**, and **13o**, the reactions were carried out in a double scale. For **13b** and **13k**, the reactions were carried out for 5 d. The isolated yields were based on α-keto acids **11**. The ee's were determined by chiral HPLC analysis after the amino acids were converted into the corresponding methyl ester for **13a** and *N*-benzoyl-protected methyl esters for **13b−o**. The absolute configurations of **13b**, **13j**, and **13o** were assigned as *R* by comparison of their optical rotations with the reported ones (ref 18). The absolute configurations of other amino acids were tentatively proposed by analog.

seems to have little influence on the reactivity, but caused a dramatic decrease of the enantioselectivity.

A plausible mechanistic pathway has been proposed for the transamination (Scheme 4).[5b,11] The pyridoxamine **3** condenses with α-keto acid **11** to form a Schiff base **15**. The ketimine **15** undergoes an asymmetric 1,3-proton transfer via a delocalized azaallylanion **16** to give an aldimine **17**, which is further hydrolyzed to the amino acid product **13** and the corresponding chiral pyridoxal **18**. The pyridoxal **18** is then reconverted to the pyridoxamine **3** by condensation with the amine source **12** to form Schiff base **19**, decarboxylation of compound **19** generates azaallylanion **20**,[19] and protonation of the anion **20** occurs at the pyridine-4-ylmethenyl carbon, followed by subsequent hydrolysis of the ketimine **21**, finishing a catalytic cycle for the transamination.

In summary, a class of new chiral pyridoxamines **3a−g** bearing a side chain has been developed from diethyl maleate **4** and ethoxyoxazole **5** via multiple steps. In the presence of the

Scheme 4. Proposed Mechanistic Pathway for the Pyridoxamine-Catalyzed Transamination



pyridoxamine **3e** as the catalyst, various α-keto acids were asymmetrically transaminated with 2,2-diphenylglycine (**12**) as the amine source under very mild conditions to give biologically and chemically important α-amino acids in 47−90% yields with 63−87% ee's. An interesting effect of the chiral side chain on enantioselectivity was observed in the asymmetric transamination. Further studies on detailed mechanisms and developing a more efficient catalytic process 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.6b01714.

Procedures for synthesis of compounds **3** and transamination of α-keto acids, characterization data, and X-ray data and NMR spectra along with HPLC chromatograms (PDF)

Crystallographic data for (*S*,*R*)-**8** (CIF)

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Notes

The authors declare no competing financial interest.

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