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A new type of chiral-pyridoxamines for catalytic asymmetric transamination of α-keto acids

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ABSTRACT

A new type of chiral pyridoxamines bearing an adjacent chiral stereocenter has been developed via multi-step synthesis. The pyridoxamines displayed catalytic activity in asymmetric transamination of α-keto acids to give a variety of optically active amino acids in 27–78% yields with 34–62% ee's under very mild conditions. This work provides a synthetic strategy to construct new chiral pyridoxamines using bromopyridine **7** as a key synthon and also represents an early example of the applications of chiral pyridoxamines in asymmetric catalysis.

Transamination of α-keto acids is a significant process to generate various amino acids in biological systems.[1] In the biological transamination, pyridoxal/pyridoxamine 5′-phosphates play a crucial role by serving as coenzymes of transaminases. Biomimetic asymmetric transamination of α-keto acids employing chiral pyridoxals/pyridoxamines has received much attention since the 1970s,[2–8] because such transamination is not only helpful to understand the biological process[2,3] but also represents a highly attractive strategy for the synthesis of optically active amino acids.[4–10] Most of the studies use stoichiometric chiral pyridoxamine derivatives as amine sources,[4] i.e., transferring the NH_2 group from the chiral pyridoxamine to a α-keto acid to form a chiral amino acid along with the corresponding pyridoxal.[1,2] Many elegant works on this chemistry have been achieved by Breslow[4b,e,f,h–j,m–q] and Kuzuhara,[4a,c,d,g,k] however, asymmetric transamination catalyzed by chiral pyridoxals/pyridoxamines, imitating the complete process of biological transamination, has been rarely reported and still remains a big challenge in organic chemistry.[7,8] We recently developed a chiral pyridoxal **5** prepared from pyridoxine and (*S*)-α,α-diarylprolinol and successfully realized **5**-catalyzed asymmetric transamination of α-keto acids **1** with 2,2-diphenylglycine (**2**) as the amine source to give various optically active α-amino acids in good yields with moderate to high ee's (Scheme 1).[10a] As in biological systems, the pyridoxal catalyst is the key for the reaction in terms of activity and enantioselectivity, thus searching for new chiral pyridoxals/pyridoxamines would be highly significant for the development of the biomimetic transamination. It has been demonstrated that the electron-attracting pyridine ring, the phenolic hydroxyl group, and the 4-formyl or CH_2NH_2 group are the necessary functional moieties for pyridoxal or pyridoxamine to implement the transamination catalysis.[11] Therefore, it is a feasible solution to install an appropriate chiral group at the 5-position of the pyridine ring to form chiral pyridoxal/pyridoxamine catalysts for asymmetric transamination. Considering the fact that the chiral center of the pyridoxamine **5** is relatively far away from the catalysis center, we designed and synthesized a class of new chiral pyridoxamines **6** with an adjacent stereogenic center and then applied the pyridoxamines into catalytic asymmetric transamination of α-keto acids. Herein, we wish to report our preliminary results on the project in this Letter.

The synthesis of pyridoxamines **6** is shown in Scheme 2. Bromopyridine **7** was treated with *n*-butyllithium at −78 °C to in situ generate pyridinyllithium which underwent nucleophilic addition toward chiral *N*-(*tert*-butylsulfinyl)imine **8** to give a pair of diastereomers (*S*,*S*)-**9** and (*R*,*S*)-**9** in a good yield with low diastereoselectivity. For example, when (*S*)-*N*-(biphenyl-2-ylmethylene)-2-methylpropane-2-sulfinamide (**8g**) was applied, the two isomers (*R*,*S*)-**9g** and (*S*,*S*)-**9g** were prepared in a 75% yield with a 2:1 diastereoselectivity (Supporting information). The two diastereomers can be separated by flash column chromatography. The major diastereomer was treated with HCl to selectively

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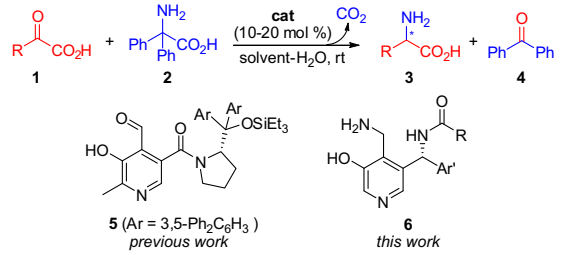
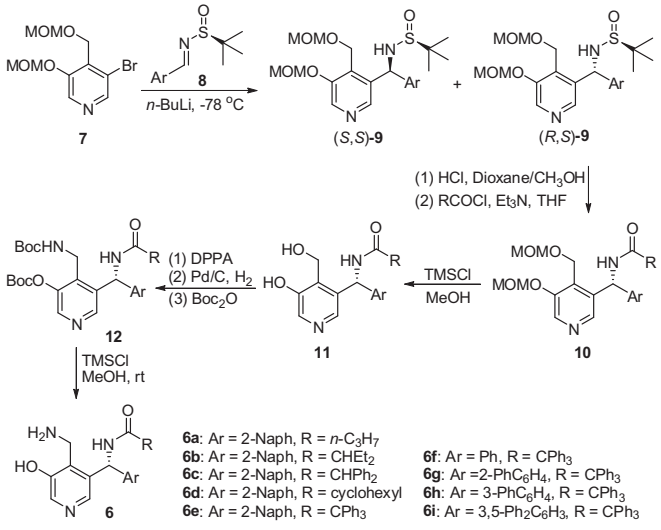


Scheme 1.



Scheme 2. Synthesis of chiral pyridoxamines **6a**–**i**.

remove the *tert*-butylsulfinyl group, followed by reaction with acyl chloride to give compound **10**. According to single-crystal X-ray (CuK_α) analysis (Fig. 1), the structure of **10g** (Ar = 2-PhC_6H_3, R = CPh_3) was further confirmed and its absolute configuration was assigned as *R*. The two MOM groups of **10** were cleanly removed with acid. Compounds **11** were treated with diphenylphosphoryl azide (DPPA) and then hydrogenated to form the corresponding pyridoxamines **6**. For **6a**, **6e**–**f**, and **6h**–**i**, the pure pyridoxamines were directly obtained by precipitation of the corresponding pyridoxamine-HCl salts from HCl solution in ethyl ether after the hydrogenative reduction. However, pyridoxamines **6b**–**d** and **6g** were difficult to be purified by the precipitation method, thus they were further converted into Boc-protected pyridoxamines **12** for chromatographic purification. Compounds **12** were then submitted to deprotection with TMSCl/MeOH to give pure pyridoxamines **6b**–**d** and **6g** as HCl salts.

In the preparation of pyridoxamines **6**, the major diastereomer of intermediates **9** was used for the following synthesis merely because of the more amount of the compound. The catalyst only has one stereogenic center after removal of the *tert*-butylsulfinyl group, therefore, the chiral pyridoxamine derived from the minor diastereomer theoretically could inverse the enantioselectivity in asymmetric transamination, but the catalyst should display the same performance in terms of catalytic activity and capability of chiral induction. The absolute configuration of pyridoxamine **6g** was assigned as *R* based on the single-crystal X-ray structure of **10g** (Fig. 1), but the absolute configurations of **6a**–**f** and **6h**–**i** were not determined.

With the chiral pyridoxamines **6a**–**i** in hand, we then investigated their catalytic activity in asymmetric transamination of α-keto acids (Table 1). Using 20 mol% of **6a** as the catalyst, the reaction of 4-(naphthalen-1-yl)-2-oxobutanoic acid (**1a**) with 2,2-diphenylglycine (**2**)[12–14] occurred smoothly under mild conditions to give the corresponding amino acid **3a** in 61% yield and 15% ee (Table 1, entry 1). Under similar conditions, catalysts **6b**–**i** were also examined (Table 1, entries 2–9). The pyridoxamine **6g** displayed the highest enantioselectivity in the transamination (Table 1, entry 7). Further studies showed that a mixed system of MeOH and H_2O (8:2) was the optimal solvent for the reaction as judged by enantioselectivity (Table 1, entry 15 vs 10–14 and 16).

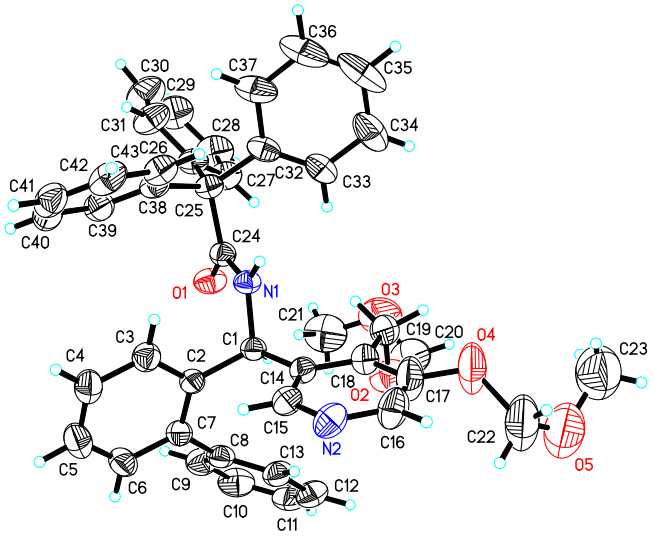


Figure 1. X-ray structure of compound *R*-**10g**.

Under the established optimal conditions, substrate scope was investigated using 10 mol% of **6g** as the catalyst (Table 2). A variety of α-keto acids were smoothly transaminated with 2,2-diphenylglycine (**2**) to give the corresponding α-amino acids in low to good yields with promising ee's. The ee can be further improved via recrystallization if desired. For example, recrystallization of **3j** in methanol/ethanol gave the amino acid in 40% yield with 88% ee. γ-Substituted α-keto acids such as 4-methyl-2-oxopentanoic acid and 4,4-dimethyl-2-oxopentanoic acid exhibited relatively higher enantioselectivity in the reaction (Table 2, for **3h** and **3k**). However, as the recently-reported chiral pyridoxal **5**, pyridoxamine catalyst **6g** also is less effective for sterically bulky substrates such as 2-oxoisovaleric acid and 2-oxo-2-phenylacetic acid in the asymmetric transamination.

In summary, we have developed a class of new chiral pyridoxamines **6a**–**i** containing an adjacent stereocenter via a multi-step synthesis from bromopyridine **7** and *N*-(*tert*-butylsulfinyl)imines **8** (Scheme 2). With 10 mol% of pyridoxamine **6g** as catalyst, various α-keto acids were transaminated in MeOH–H_2O at room temperature, giving the corresponding chiral α-amino acids **3a**–**k** in 27–78% yields with 34–62% ee's. This work provides a synthetic strategy to construct new chiral pyridoxamine catalysts using bromopyridine **7** as a key synthon and also demonstrates an application of chiral pyridoxamines in asymmetric catalysis.[16] Further studies on development of more efficient catalysts for asymmetric transamination, mechanistic studies of the reaction, and exploring new catalytic applications of chiral pyridoxals/pyridoxamines are currently underway.

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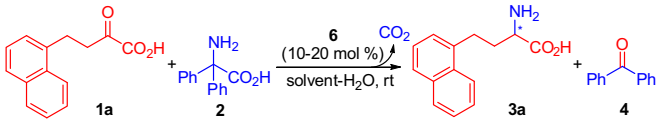
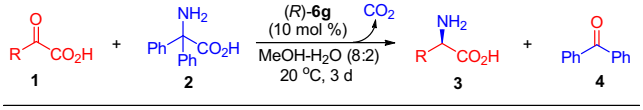
Table 1
Optimization of reaction conditions for the asymmetric transamination[a]

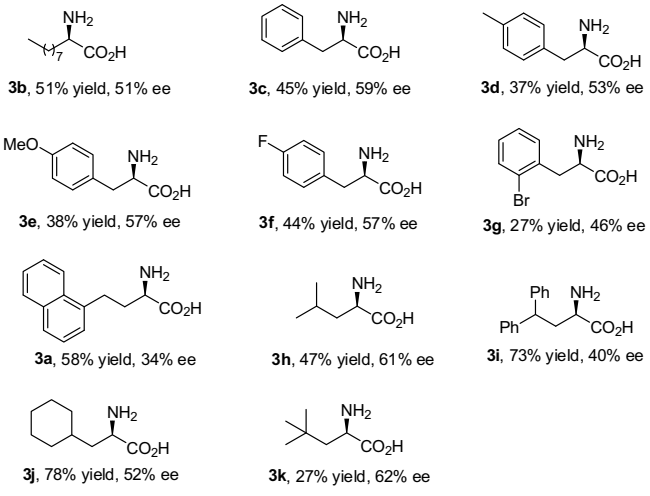


Entry	Cat.	Solvent	Yield[b] (%)	ee[c] (%)
1	**6a**[d]	MeOH/H_2O (9:1)	61	15 (+)
2	**6b**[d]	MeOH/H_2O (9:1)	62	22 (+)
3	**6c**[d]	MeOH/H_2O (9:1)	70	22 (+)
4	**6d**[d]	MeOH/H_2O (9:1)	21	10 (+)
5	**6e**[d]	MeOH/H_2O (9:1)	74	27 (+)
6	**6f**[d]	MeOH/H_2O (9:1)	91	31 (−)
7	(*R*)-**6g**	MeOH/H_2O (9:1)	74	34 (−)
8	**6h**[d]	MeOH/H_2O (9:1)	73	30 (−)
9	**6i**[d]	MeOH/H_2O (9:1)	78	27 (−)
10[e]	(*R*)-**6g**	THF/H_2O (9:1)	54	17 (−)
11[e]	(*R*)-**6g**	DMF/H_2O (9:1)	50	23 (−)
12[e]	(*R*)-**6g**	Toluene/H_2O (9:1)	36	10 (−)
13[e]	(*R*)-**6g**	DCM/H_2O (9:1)	47	10 (−)
14[e]	(*R*)-**6g**	CH_3CN/H_2O (9:1)	48	20 (−)
15[e]	(*R*)-**6g**	MeOH/H_2O (8:2)	50	34 (−)
16[e]	(*R*)-**6g**	MeOH/H_2O (6:4)	31	11 (−)

[a] All the reactions were carried out with α-keto acid **1a** (0.10 mmol), 2,2-diphenylglycine (**2**) (0.10 mmol), and catalyst **6** (0.020 mmol) in solvent (1.0 mL) at 20 °C for 40–48 h (48 h for entries 1–9, 45 h for entries 10–14, and 40 h for entries 15 and 16) unless otherwise stated.
[b] Isolated yield based on α-keto acid **1a**.
[c] The ee's were determined by chiral HPLC after the amino acid **3a** was converted into the corresponding methyl ester.
[d] The absolute configurations of the catalysts were not determined.
[e] Catalyst **6g** (0.010 mmol) was used.

Table 2
Asymmetric transamination of α-keto acids[a]





[a] All the reactions were carried out with α-keto acids **1** (0.30 mmol), **2** (0.30 mmol), catalyst (*R*)-**6g** (0.030 mmol) in MeOH–H_2O (8:2) (0.1 M for **1**) at 20 °C for 3 d unless otherwise stated. For **3a** and **3i**, the reactions were employed on 0.2 mmol scale. The isolated yields were based on α-keto acids **1**. The ee's were determined by chiral HPLC analysis after the amino acids were converted into the corresponding methyl ester for **3a** and *N*-protected esters for **3b**–**k**. The absolute configurations of **3c**, **3h**, and **3j** were assigned as *R* by comparison of their optical rotations with the reported ones (ref. 15). The absolute configurations of other amino acids were tentatively determined by analogy.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.09.005.

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