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Enantioselective biomimetic transamination of α-keto acids catalyzed by H_4-naphthalene-derived axially chiral biaryl pyridoxamines

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ABSTRACT

Asymmetric biomimetic transamination is a highly attractive method for synthesis of chemically and biologically important chiral amino acids and chiral amines. Development of chiral pyridoxamines/pyridoxals is the key for the reaction. New axially chiral biaryl pyridoxamines based on H_4-naphathene skeleton have been developed. The pyridoxamines display good enantioselectivity and high catalytic activity in asymmetric biomimetic transamination of α-keto acids, affording various optically active unnatural amino acids in 61–98% yields with up to 91% ee's.

Chiral α-amino acids are one type of the most important molecules.[1,2] They not only serve as basic building units of proteins but also are widely present in various biologically active molecules such as natural product Vancomycin,[3] antiasmatic drug FK-888,[4] and antitumor drug Abarelix[5] (Scheme 1).[1] In biological systems, enzymatic transamination of α-keto acids is the main way to synthesize various chiral α-amino acids.[6] The reaction is catalyzed by the coenzyme pyridoxal/pyridoxamine phosphates, i.e. vitamin B_6 (Scheme 2).[6,7] Pyridoxamine phosphate (PMP) condenses with α-keto acid **1** to form a ketimine intermediate, which then undergoes asymmetric 1,3-H shift and subsequent hydrolysis to give chiral amino acid **2** and generate pyridoxal phosphate (PLP). The catalyst pyridoxal is re-converted back to pyridoxamine (PMP) by amine source **2′** via a reverse transamination process, completing a catalytic cycle. Mimicking the biological process with chiral pyridoxals/pyridoxamines[8–14] as the catalyst provides an attractive strategy for the synthesis of chiral amino acids. The pyridoxal/pyridoxamine catalyst plays a crucial role in asymmetric biomimetic transamination in terms of activity and enantioselectivity. Recently, we have developed several chiral pyridoxal/pyridoxamine catalysts and also have realized the corresponding catalytic asymmetric biomimetic transamination for the first time.[15] It has been found that chiral pyridoxamine **3** displays the highest catalytic activity and the best enantioselectivity in asymmetric transamination of α-keto acids among the catalysts developed.[15c] The axially chiral biaryl skeleton probably accounts for its good catalytic performance. In order to pursue more efficient catalysts for asymmetric biomimetic transamination, we developed new axially chiral biaryl pyridoxamines **4** containing partially hydrogenated naphthalene moiety (Scheme 3) and also investigated **4**-catalyzed asymmetric transamination of α-keto acids. Herein, we report our studies on this project.

The synthesis of chiral pyridoxamines **4** started with Pd-catalyzed Suzuki coupling of pyridyl bromide **5** and H_4-naphthyl boronic acid **6** to give dialdehyde **7** in 31% yield, building the skeleton of the catalyst (Scheme 4). Selective formation of imine with (*S*)-*tert*-butanesulfinamide followed by reduction with $NaBH_4$ formed a pair of chromatographically separable diastereomers (*R*,*S*)-**8** and (*S*,*S*)-**8**. The absolute configurations of the diastereomers were determined by X-ray analysis of the oxime derivative [(*S*,*S*)-**9-oxime**] of compound (*S*,*S*)-**9**,[16] which was obtained from (*S*,*S*)-**8** by oxidation with MnO_2 and subsequent condensation with hydroxylamine (Fig. 1). Compound (*R*,*S*)-**8** then underwent oxidation with MnO_2, reductive amination, and deprotection to give the desired chiral pyridoxamines **4a-e** as HCl salts.

By using 5 mol% of chiral pyridoxamine **4a** as the catalyst and 2,2-diphenylglycine (**11**)[17–19] as the amine source, transamination of α-keto acid **1a** was optimized (Table 1). The transamination in ethanol and water (8:2) displayed the highest enantioselectivity (Table 1, entry 2 vs 1 and 3–10). A certain amount of water seems

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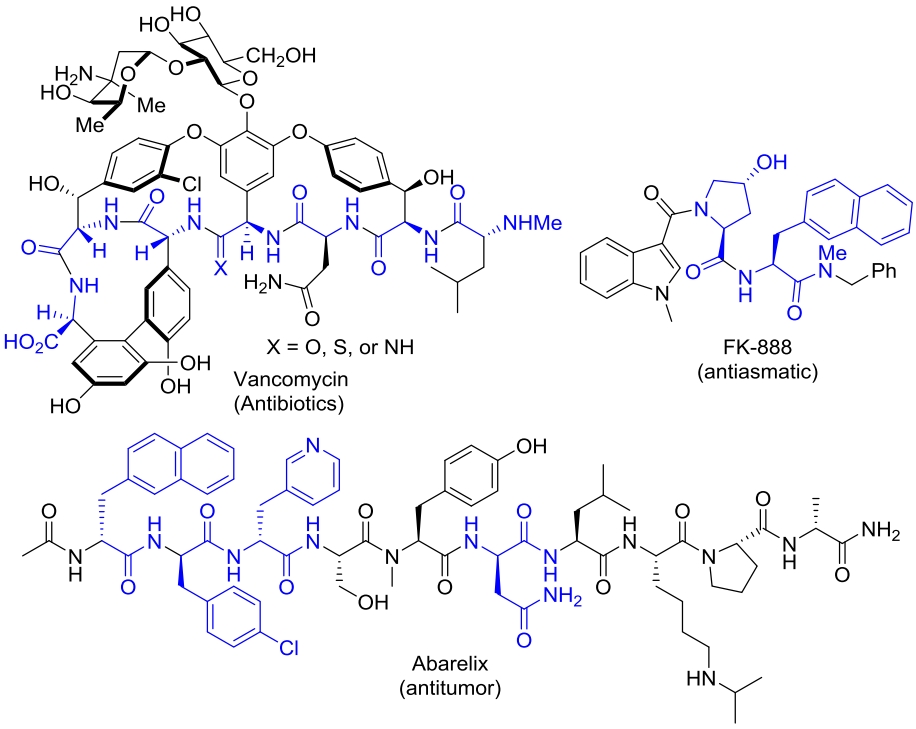
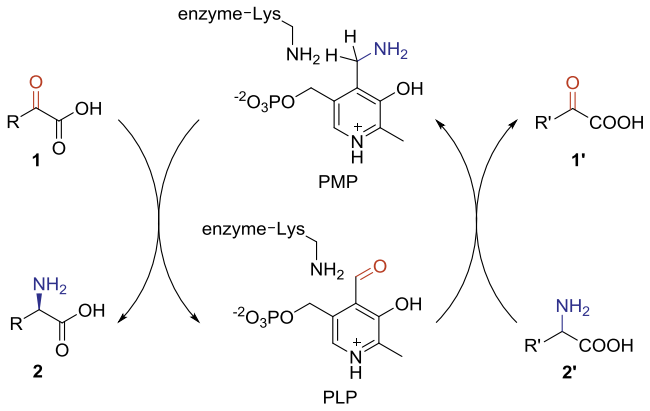
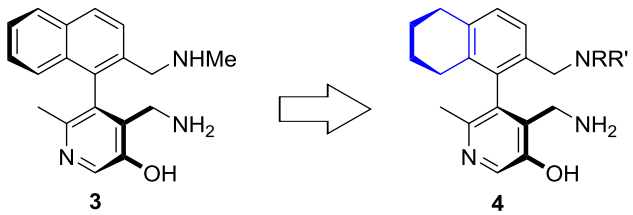


Scheme 1. Biologically active molecules containing amino acid moieties.



Scheme 2. Biological transamination of α-keto acids.



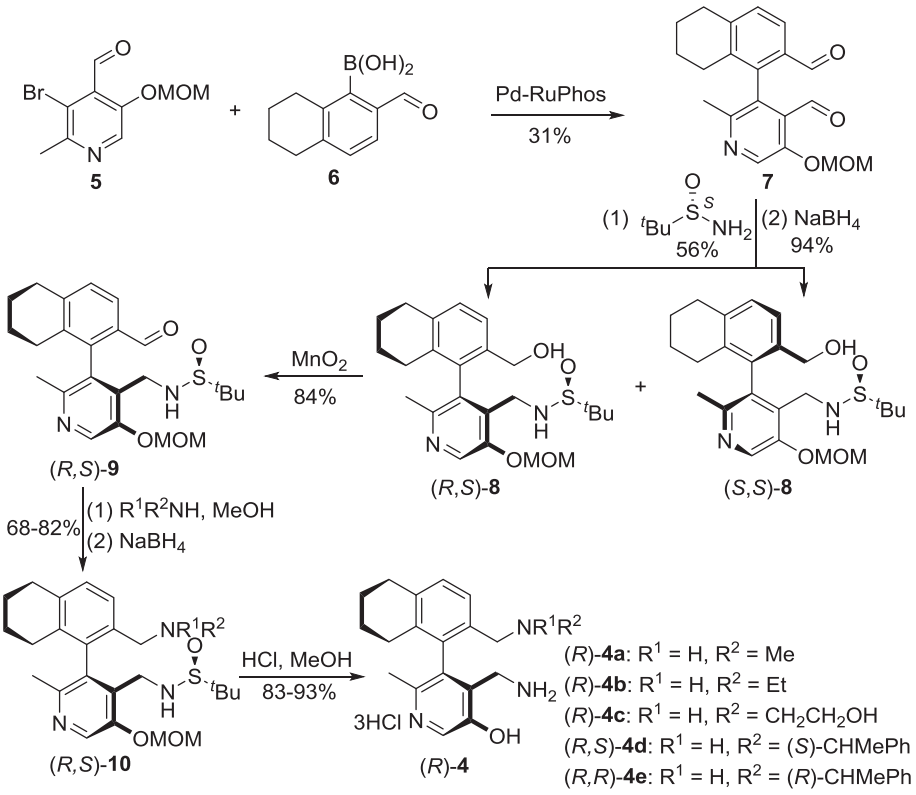
Scheme 3. Design of new chiral pyridoxamines (**4**).

important to the reaction. Transamination became very slow in the absence of water (Table 1, entry 11 vs 2 and 12–13). Introduction of additive HOAc (8 equiv.) resulted in increased isolated yield (Table 2, entry 15 vs 2 and 14). The chiral pyridoxamines **4b–e** were also examined for the asymmetric transamination and pyridoxamine **4a** containing a MeNH side chain was the most efficient in terms of catalytic activity and enantioselectivity (Table 1, entry 16 vs 17–20).

Under the optimized reaction conditions, substrate scope for the asymmetric transamination of α-keto acids was then examined in the presence of 5 mol% of chiral pyridoxamine (*R*)-**4a** (Table 2). Various substrates including aliphatic linear (**1b–f**), aromatic linear (**1a** and **1g–i**), and γ-substituted (**1j–n**) α-keto acids were all successfully transaminated to give the corresponding chiral α-amino acids in 61–98% yields with 72–91% ee's (Table 2, entries 1–14). For α-keto acid containing a chiral center such as **1o**, the resulting α-amino acid **2o** was obtained with good diastereoselectivity (93:7) (Table 1, entry 15). Various functional groups such as Cl (**1c**), Br (**1d**), OTBDPS (**1f**), and C–C double bond (**1o**) were all well tolerated in the asymmetric transamination.

A plausible mechanism has been proposed for the asymmetric transamination (Scheme 5). Condensation of pyridoxamine **4a** with α-keto acid **1** forms Schiff base **12**. The intermediate **12** undergoes asymmetric 1,3-H shift to give aldimine **14** under the assistant of the amine side arm which serves as a base to promote deprotonation of the imino C–H of **12** and thus accelerates the transamination process. Hydrolysis of the aldimine affords chiral amino acid **2** as well as the corresponding pyridoxal. The pyridoxal is supposed to be immediately converted to internal iminium **15** by in situ intramolecular condensation. The iminium **15** then undergoes decarboxylative transamination with 2,2-diphenylglycine (**11**) as the amine source to regenerate pyridoxamine catalyst **4a**, completing a catalytic cycle. The whole catalytic pathway has perfectly mimicked biological transamination process.

In summary, we have developed a new type of chiral pyridoxamines **4a–e** containing H_4-naphthene-based biaryl structural skeleton. The chiral pyridoxamines displayed good activity and enantioselectivity in asymmetric transamination of α-keto acids, to give a variety of chemically and biologically important chiral



Scheme 4. Synthesis of chiral pyridoxamines **4a–e**.

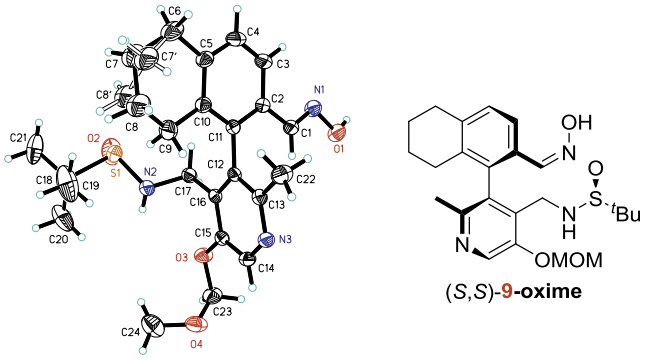


Fig. 1. X-ray structural analysis of [(*S*,*S*)-**9-oxime**]

α-amino acids in 61–98% yields with 72–91% ee's. Further studies on development of more efficient asymmetric processes are currently underway.

Acknowledgments

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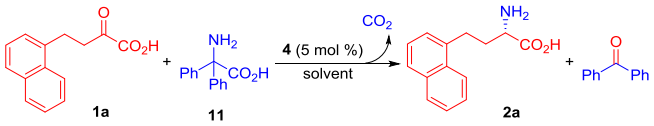
A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.089.

Table 1
Catalyst screening and condition optimization.[a]



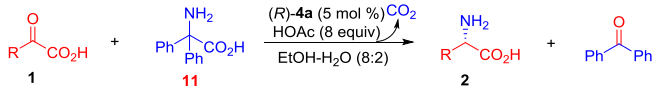
Entry	Cat.	Solvent	HOAc	Yield[b] (%)	ee[c] (%)
1	**4a**	MeOH-H_2O (8:2)	1 equiv	92	79
2	**4a**	EtOH-H_2O (8:2)	1 equiv	74	83
3	**4a**	^{i}PrOH-H_2O (8:2)	1 equiv	76	56
4	**4a**	^{t}BuOH-H_2O (8:2)	1 equiv	58	78
5	**4a**	CF_3CH_2OH-H_2O (8:2)	1 equiv	57	79
6	**4a**	THF-H_2O (8:2)	1 equiv	57	63
7	**4a**	CH_3CN-H_2O (8:2)	1 equiv	74	59
8	**4a**	Toluene-H_2O (8:2)	1 equiv	trace	–[d]
9	**4a**	DMF-H_2O (8:2)	1 equiv	60	38
10	**4a**	DCM-H_2O (8:2)	1 equiv	trace	–[d]

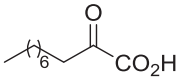
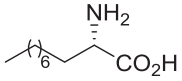
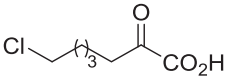
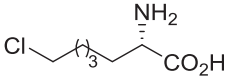
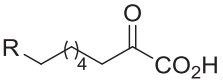
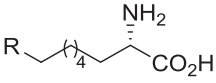
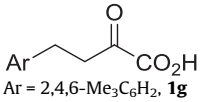
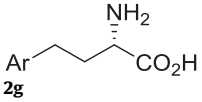
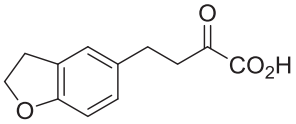
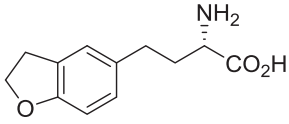
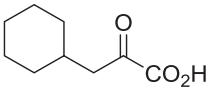
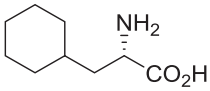
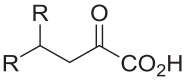
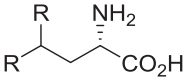
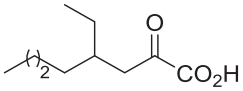
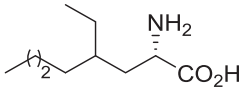
Table 1 (*continued*)

Entry	Cat.	Solvent	HOAc	Yield[b] (%)	ee[c] (%)
11	**4a**	EtOH	1 equiv	trace	–[d]
12	**4a**	EtOH-H_2O (9:1)	1 equiv	61	80
13	**4a**	EtOH-H_2O (7:3)	1 equiv	53	77
14	**4a**	EtOH-H_2O (8:2)	0 equiv	86	82
15	**4a**	EtOH-H_2O (8:2)	8 equiv	93	83
16[e]	**4a**	EtOH-H_2O (8:2)	8 equiv	96	83
17[e]	**4b**	EtOH-H_2O (8:2)	8 equiv	75	83
18[e]	**4c**	EtOH-H_2O (8:2)	8 equiv	77	82
19[e]	**4d**	EtOH-H_2O (8:2)	8 equiv	50	77
20[e]	**4e**	EtOH-H_2O (8:2)	8 equiv	73	83

[a] All the reactions were carried out with **1a** (0.10 mmol), 2,2-diphenylglycine **11** (0.10 mmol), **4** (0.0050 mmol), and HOAc in solvent (0.50 mL) at rt for 24 h unless otherwise stated.
[b] Isolated yield based on **1a**.
[c] Determined by chiral HPLC analysis of the corresponding methyl ester of **2a**.
[d] Not determined.
[e] The reaction was carried out in EtOH-H_2O (8:2) (1.0 mL).

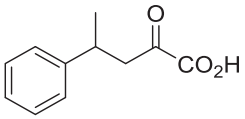
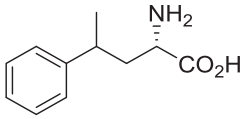
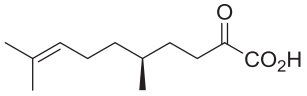
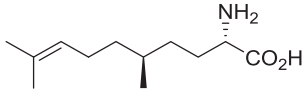
Table 2
(*R*)-**4a**-catalyzed asymmetric transamination.[a]



Entry	1	2	Yield (%)[b]	ee (%)[c]
1	 **1b**	 **2b**	70	83
2	 **1c**	 **2c**	74	76
				
3	R = Br, **1d**	**2d**	71	80
4	R = OPh, **1e**	**2e**	67	74
5	R = OTBDPS, **1f**	**2f**	61	81
				
6	Ar = 2,4,6-$Me_3C_6H_2$, **1g**	**2g**	77	78
7	Ar = 2-PhC_6H_4, **1h**	**2h**	79	84
8	Ar = 1-Naphthyl, **1a**	**2a**	96	83
				
9	**1i**	**2i**	63	83
				
10	**1j**	**2j**	76	84
				
11	R = Et, **1k**	**2k**	68	91
12	R = Ph, **1l**	**2l**	98	75
13	 **1m**	 **2m**	68	(1:1)[d] 86/86

(*continued on next page*)

Table 2 (*continued*)

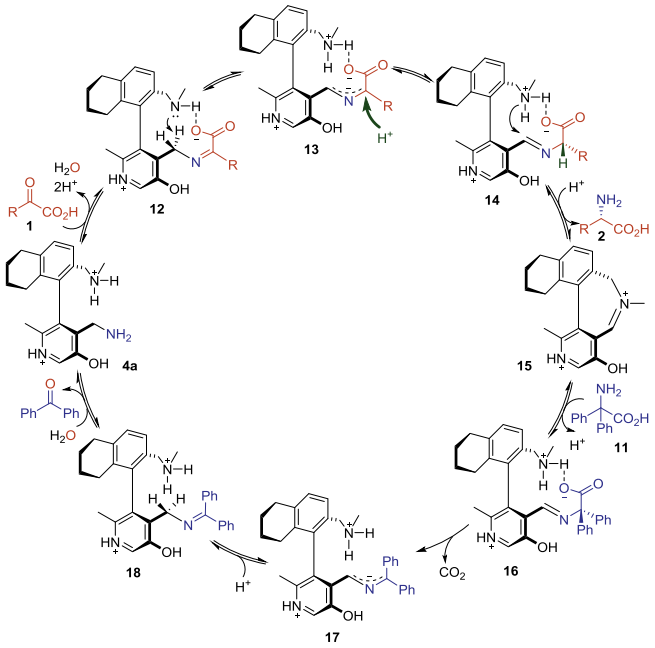
Entry	1	2	Yield (%)[b]	ee (%)[c]
14	 **1n**	 **2n**	64	(1:1.1)[d] 85/73
15	 **1o**	 **2o**	69	93:7[d]

[a] All the reactions were carried out with **1** (0.10 mmol), **11** (0.10 mmol), (*R*)-**4a** (0.0050 mmol), and HOAc (0.80 mmol) in EtOH (0.80 mL) and H_2O (0.20 mL) at rt for 24 h unless otherwise stated. The reaction time was 32 h for **1c-d** and 36 h for **1e** and **1m**.

[b] Isolated yield based on **1**.

[c] The ee's were determined by chiral HPLC analysis of the corresponding methyl ester for **2a** and the *N*-benzoyl-protected methyl esters for **2b**–**n**. The absolute configurations of **2a**–**b** were assigned as *S* by comparison of HPLC elution order of enantiomers with the reported ones (Ref. 15c). The absolute configurations of other amino acids were proposed by analog.

[d] The dr values were determined by chiral HPLC analysis of the corresponding *N*-benzoyl-protected methyl esters of **2m**–**o**.



Scheme 5. Proposed mechanistic pathway.

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