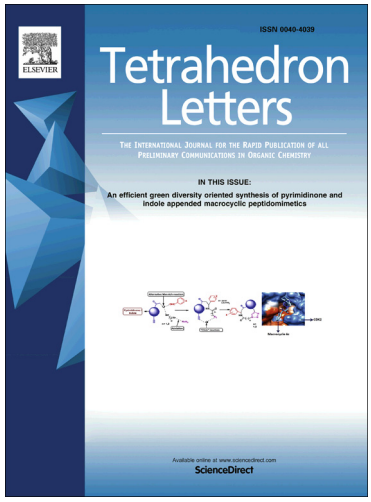

Unnatural Tripeptide as Highly Enantioselective Organocatalyst for Asymmetric Aldol Reaction of Isatins

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Unnatural Tripeptide as Highly Enantioselective Organocatalyst for Asymmetric Aldol Reaction of Isatins

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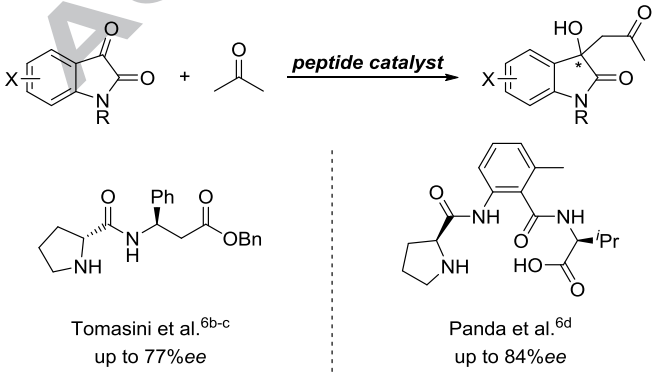
ABSTRACT

The development of unnatural tripeptides as highly enantioselective organocatalysts for the asymmetric aldol reaction of isatins was achieved. H-Pro-Gly-D-Ala-OH with the D-alanine residue as the C-terminal amino acid residue expressed the best enantioselectivity. The H-Pro-Gly-D-Ala-OH-catalyzed reaction of isatins gave various aldol adducts with up to 93% yield and up to 97% ee. Investigation of the transition state via DFT calculation revealed that high optical purity was realized by the D-alanine controlled steric environment.

Organocatalysts are useful asymmetric catalysts in synthetic chemistry because they are environment-friendly, inexpensive and easy to use.[1] In particular, the development of organocatalysts that display high enantioselectivity to the asymmetric aldol reaction has received attention as this reaction is one of the most useful carbon-carbon forming reactions.[2] As pioneering work, List et al. reported proline-catalyzed asymmetric aldol reaction of aldehydes.[3] So far, various prolinamide catalysts that displayed high enantioselectivity to asymmetric aldol reaction were developed.[2]

In prolinamide catalysts, peptide catalysts are recognized as helpful catalysts for asymmetric aldol reaction as it is possible to realize high enantioselectivity and high activity by optimization of amino acid sequence. However, although peptides that catalyze aldol reaction using aldehydes as aldol accepter with high enantioselectivity are reported,[4,5] peptides that catalyze aldol reaction using ketones as aldol accepter are limited.[6] Especially, peptide catalysts for asymmetric aldol reaction of isatins giving 3-substituted 3-hydroxy-2-oxindoles which is a partial structure in various biologically active compounds are only two reports.[7]

Figure 1. Peptide-catalysts for asymmetric aldol reaction of isatins



Tomasini et al. described the dipeptide-catalyzed asymmetric aldol reaction of isatins, with up to 77% *ee* (Figure 1, left).[6b-c] Panda et al. reported the anthranilic acid-containing tripeptide-catalyzed asymmetric aldol reaction of isatins with up to 84% *ee* (Figure 1, right).[6d] These peptide catalysts for this reaction are expected to improve stereoselectivity.

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In this work, to develop a highly enantioselective peptide catalyst for the asymmetric aldol reaction of isatins, we designed unnatural tripeptide catalysts containing D-amino acid (Figure 2).

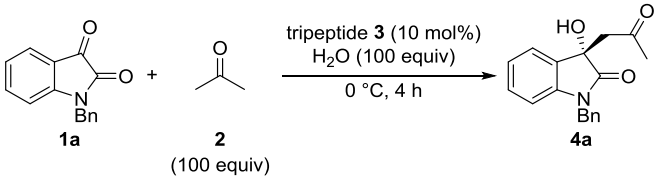
Figure 2. catalyst design

The concept of catalyst design was stereocontrol by D-amino acid. We thought that high enantioselectivity could be realized by a tripeptide that took a different conformation than a tripeptide composed of only natural L-amino acids by introducing an D-amino acid in the amino acid sequence. This catalyst had an amino group that acted as enamine formation site to activate a nucleophile as well as two amido groups and carboxyl group as hydrogen bonding sites to activate an electrophile. For that reason, we expected that this catalyst was active enough for this reaction.

Tripeptides used as catalysts in this reaction were synthesized by a method suggested in the supporting information (see supporting information).

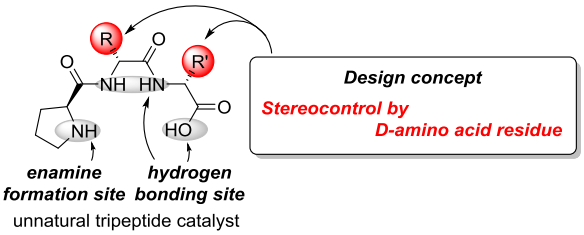
The effect of the catalyst design in the asymmetric aldol reaction of isatins was examined using a reaction between N-benzylisatin **1a** and acetone **2** as model reaction (Table 1). To clarify the effect of introducing D-amino acid as the C-terminal amino acid residue, aldol reactions catalyzed by **3a**, **3b**, and **3c** having glycine, L-alanine, and D-alanine as C-terminal amino acid residue were carried out (Table 1, entries 1-3). The aldol reaction catalyzed by **3c** (with D-alanine as C-terminal amino acid residue) had the best enantioselectivity (Table 1, entry 3). The aldol reactions catalyzed by **3d** and **3e** (having bulky isopropyl or aromatic phenyl substitution) showed lower optical purity than the **3c**-catalyzed aldol reaction (Table 1, entries 4 and 5). To reveal the effect of introducing a D-amino acid at the amino acid residue adjacent to the proline residue, aldol reactions catalyzed by **3f** and **3g** (having L-alanine and D-alanine as amino acid residues adjacent to proline residue) were conducted (Table 1, entries 6 and 7). The stereoselectivities of both the reactions did not improve relative to the **3c**-catalyzed aldol reaction. These results indicated that C-terminal D-alanine was beneficial for enantioselectivity. To investigate the effects of N-terminal amino group and C-terminal carboxyl group, aldol reactions catalyzed by **3h** and **3i** were carried out (Table 1, entries 8 and 9). **3h**-catalyzed reaction did not progress. The enantioselectivity and chemical yield of **3i**-catalyzed reaction dropped relative to the **3c**-catalyzed reaction. it was concluded that **3c** was the optimal catalyst for this reaction.

Table 1. Optimization of catalyst



Entry	tripeptide **3**	Yield (%)[a]	*ee* (%)[b]
1	H-Pro-Gly-Gly-OH **3a**	99	71
2	H-Pro-Gly-Ala-OH **3b**	86	61
3	H-Pro-Gly-D-Ala-OH **3c**	99	91
4	H-D-Pro-Gly-Val-OH **3d**	66	-58
5	H-D-Pro-Gly-Phg-OH **3e**	99	-89
6	H-Pro-D-Ala-D-Ala-OH **3f**	99	76
7	H-Pro-Ala-D-Ala-OH **3g**	99	86
8	Cbz-Pro-Gly-D-Ala-OH **3h**	N.R.	N.D.
9	H-Pro-Gly-D-Ala-OMe **3i**	9	51

[a] Determined by ^{1}H NMR using internal standard technique. [b] Determined by HPLC analysis using DAICEL CHIRALPAK AD-H



The effect of reaction conditions was investigated (Table 2). The effects of reaction temperature and catalytic amount for the optical purity of aldol adduct were slight (Table 2, entries 1-5). The amounts of acetone **2** and H_2O had great influence on enantioselectivity and chemical yield (Table 2, entries 6-10). As a consequence, the **3c** (5 mol%)-catalyzed reaction in the presence of 100 eq. acetone **2** and H_2O at 0 °C for 4 h demonstrated the highest optical purity of aldol adduct (Table 2, entry 4).

After optimizing the reaction condition, the substrate scope of this reaction was studied (Figure 3).

Figure 3. peptide-catalyzed asymmetric aldol reaction of isatins

To disclose the influence of substitution on the amido group in isatins, reactions using isatin **1b**, *N*-methylisatin **1c**, and *N*-ethylisatin **1d** were conducted. Isatin **1b** gave the corresponding aldol adduct **4b** with low enantioselectivity and medium yield. Good yield and *ee* were observed by employing *N*-methylisatin **1c** and *N*-ethylisatin **1d**. To divulge the effect of the substituent on the aromatic ring in isatin, reactions using 4-bromoisatin **1e**, 5-bromoisatin **1f,** and 6-bromoisatin **1h** were performed. Although **4e** and **4f** were noticed in high yields, optical purity was low. *N*-benzyl-6-bromoisatin **1h** reacted to give the corresponding aldol adduct **1h** in high yield and enantioselectivity.

It was assumed that a catalytic cycle of this reaction was similar to the proline-catalyzed asymmetric aldol reaction (Figure 4).[3] Thus, acetone **2** (nucleophile) was activated by enamine formation due to reaction between the amino group of **3c** and **2**. C–C bond was next formed by nucleophilic addition to isatins **1** as an electrophile of enamine. Finally, the aldol adduct was given by hydrolysis of the iminium cation generated by nucleophilic addition to isatins **1** of enamine. In this reaction, absolute configuration of the aldol adduct was determined at this C–C bond formation step.

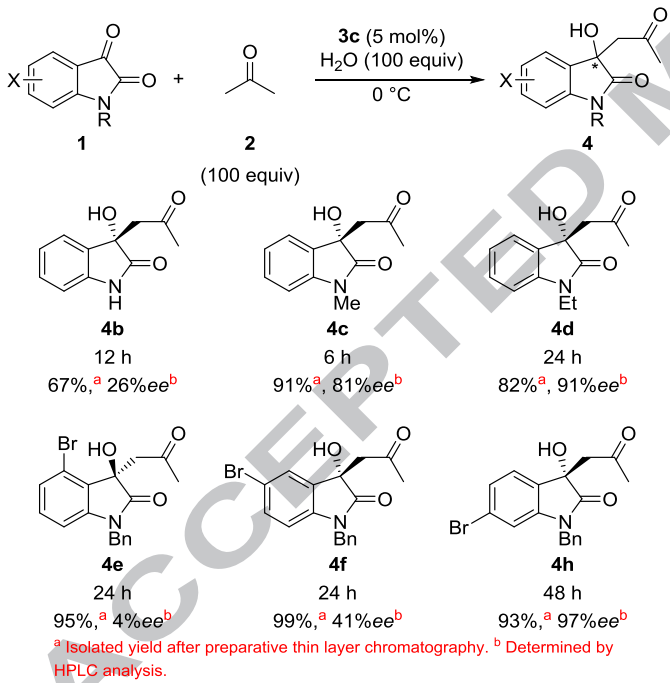


Table 2. Optimization of the reaction conditions of **3c**-catalyzed reaction between **1a** and **2.**

Entry	Temp. (°C)	Time (h)	**1c** (mol%)	Acetone (equiv)	H_2O (equiv)	Yield (%)[a]	*ee* (%)[b]
1	0	4	10	100	100	99	91
2	-40	24	10	100	100	95	89
3	25	4	10	100	100	95	87
4	0	4	5	100	100	95(92)[c]	94
5	0	4	2.5	100	100	58	89
6	0	4	5	200	100	94	84
7	0	4	5	50	100	18	40
8	0	4	5	100	200	21	57
9	0	4	5	100	50	98	81
10	0	4	5	100	None	51	21

[a] Determined by ^{1}H NMR using internal standard technique. [b] Determined by HPLC analysis using DAICEL CHIRALPAK AD-H. [c] Isolated yield after preparative thin layer chromatography.

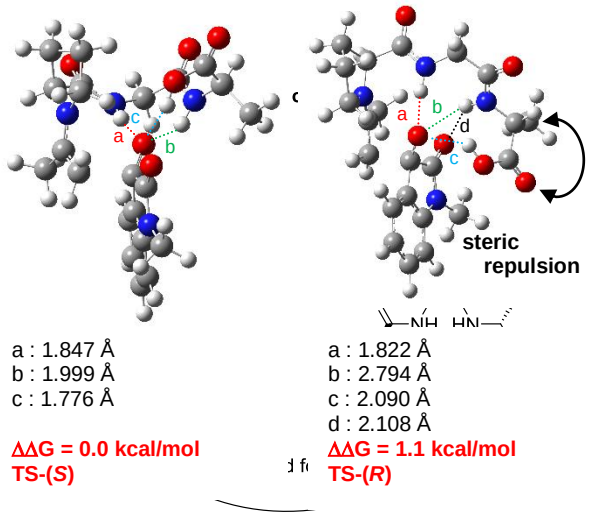


Figure 4. Plausible catalytic cycle

To reveal the role of the C-terminal D-alanine residue in **3c** for enantioselectivity, the transition state structure of C–C bond formation step was investigated via DFT calculation.[8,9] The **3c**-catalyzed aldol reaction between *N*-methylisatin **1c** and acetone **2** was selected as model reaction because of reduced calculation cost. In both cases of transition states giving the (*S*)-aldol adduct and (*R*)-aldol adduct, although two transition states possessing different hydrogen-bonding networks were found, it was disclosed that TS-(S)—with multiple hydrogen bonds such as a, b, and c—and TS-(R)—with multiple hydrogen bonds such as a, b, c, and d—were kinetically favorable (see supporting information). Comparison of the Gibbs energies of TS-(*S*) and TS-(*R*) displayed that TS-(*R*) was 1.1 kcal/mol more unstable than TS-(*S*) in spite of TS-(*R*) having more hydrogen bonds than TS-(*S*) (Figure 5). The relationship between the Gibbs energies of TS-(*S*) and TS-(*R*) was elucidated by the difference in the steric environment of the methyl group of the D-alanine residue. In TS-(*R*), the methyl group in D-alanine repelled the carboxyl group. In contrast to TS-(*R*), in TS-(*S*), the methyl group in D-alanine residue did not repel the carboxyl group or the carbonyl group in the glycine residue. We thought that this difference in steric environments destabilized only TS-(*R*), so that the unnatural tripeptide **3c** displayed high stereoselectivity in this reaction. The investigation of transition state structure via DFT calculation indicated that the C-terminal D-alanine residue in **3c** played an essential role in the production of enantioselectivity.

In conclusion, we developed unnatural tripeptide **3c** as a highly enantioselective organocatalyst for the asymmetric aldol reaction of isatins. D-alanine as the C-terminal amino acid residue in **3c** improved the optical purity of the aldol adduct. Investigation of the transition state structure via DFT calculation revealed that unnatural D-alanine residue controlled the steric environment to express high enantioselectivity.

Figure 5. Transition state of **3c**-catalyzed reaction of **1c** with **2**

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Graphical Abstract

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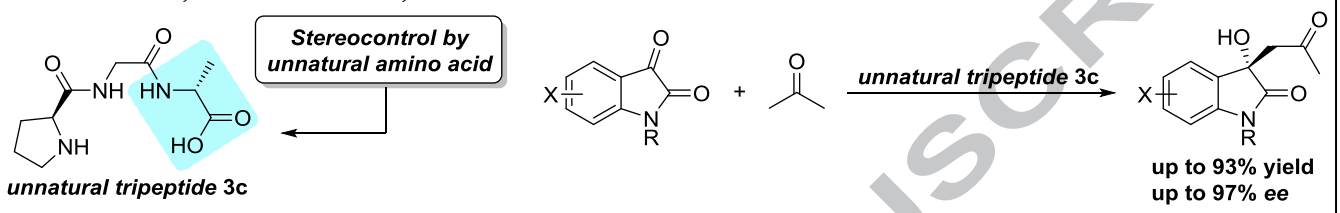

Highlights

Tripeptides containing D-amino acid were prepared.

Asymmetric Aldol reaction using our tripeptide organocatalyst.

Construction of 3-hydroxyl-2-oxindolesusing with excellent ee.