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Direct asymmetric aldol reactions in aqueous media catalyzed by a β-cyclodextrin–proline conjugate with a urea linker



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ABSTRACT

Covalently attaching proline to β -CD through a urea linkage resulted in the synthesis of a water-soluble chiral organocatalyst **1** in high yield. Catalytic asymmetric aldol condensations between aldehydes and acetone were carried out under water-containing conditions by using 5 mol % of **1** as catalyst, and moderate to high yields and enantioselectivities (up to 99% ee) were achieved for a broad range of aldehydes. Substrate selectivity was also tested. Recycling experiments were performed to confirm good recyclability and reusability of the catalyst.

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The direct asymmetric aldol reaction between ketones and aldehydes is a powerful tool for the construction of carbon-carbon bonds in synthetic organic chemistry.¹ Its great usefulness for the syntheses of natural products and valuable medicinal intermediates has promoted the rapid evolution of efficient chiral catalyst systems.² among which optically pure proline and its derivatives have proven to be a class of effective catalysts for the asymmetric aldol reactions over the past decades.³ However, in most cases the reactions were performed in organic solvents.⁴ Water is known as the important reaction media for most enzymatic reactions in living systems, and from a viewpoint of green chemistry it has obvious advantages to use water as a solvent over organic solvents that are often flammable and toxic. In addition, using water as a solvent for catalytic organic reactions also makes the catalysts recyclable and reusable. To develop enzyme mimics and to better understand the mechanism of the chemistry of life, it is desired to observe catalysts that can carry out organic transformations efficiently and selectively in water media.^{5,6} There were recent examples on the diastereo- and enantio-selective aldol reactions in water, however, the ketone substrates have been limited to cyclohexanone in many cases.⁷ In contrast, the less active acetone was rarely used for highly selective aldol reactions in water.

In recent years, β -cyclodextrin (β -CD) has been utilized as an important carrier for effective aldol organocatalysts such as proline

* Corresponding author. E-mail address: guzhang@jjay.cuny.edu (G. Zhang). derivatives to mimic enzyme catalyzed reactions in water.⁸ β-CD is water soluble, yet it has a hydrophobic cavity that mimics hydrophobic pockets in enzyme and can bind hydrophobic organic substrates in aqueous media. The pioneering work was conducted by Breslow and co-workers, who reported that assembles of β-CD and various amino moieties act as Schiff base forming aldolase mimics to catalyze aldol reactions under buffer conditions.⁹ Although a few recent examples revealed that inclusion complexes of β-CD with active proline derivatives catalyzed efficiently enantio- and diastereo-selective aldol reactions in water,¹⁰ covalently linked catalysts containing B-CD and organocatalysts for asymmetric aldol reactions in water were little reported.^{11,12} In 2012, Ji and Shen reported two pyrrolidine modified β -CDs that catalyzed aldol reactions between 4-nitrobenzaldehyde and acetone in medium yields and moderate to good ee values under buffer conditions, and the control of pH values were proven to be crucial for good stereoselectivities.¹¹ Fernández-Mayoralas and co-worker also described several proline- β -CD conjugates that were linked through various amide moieties and tested their catalytic activity toward asymmetric aldol condensations between 4-nitrobenzaldehyde and dioxanone in water, however, only moderate conversions and low enantioselectivity were achieved. Although it was observed that one of these catalysts promoted the reaction of 4-nitrobenzaldehyde and acetone with high conversion, only 6% ee was obtained.¹

Herein, we report our efforts in the synthesis of a new proline- β -CD conjugate **1** covalently linked by a urea spacer (Scheme 1),





Scheme 1. The structures of proline derived β -CD catalysts 1 and 2.

and its application as a water-soluble, effective catalyst for highly enantioselective aldol reactions between aldehydes and acetone in aqueous media. Urea and thiourea derivatives have been extensively exploited as excellent organocatalysts for many transformations, by virtue of their capacity of binding and activating substrates effectively by hydrogen bonding.¹³ However, they were thus far not utilized as linkers between β -CD and proline derivatives for organocatalysis.

The synthetic route for catalyst 1 and its TBDMS protected analog **2** is illustrated in Scheme 2 (TBDMS = *t*-butyldimethylsiloxy). The known proline derivative 4 was synthesized according to a published procedure,¹⁴ and it was then taken to react with triphosgene under basic condition to afford its isocyanate derivative, to which a known β -CD derived primary amine **3**¹⁵ was added. The efficient click reaction between the isocynate derivative and amine **3** allows the formation of a key urea-containing intermediate **5** in high yield in one pot (two steps, 81%). Starting from 5, the synthesis of **1** requires the following two deprotection steps: firstly **5** was treated with excess of solid NH₄F in methanol under refluxing condition to remove TBDMS protecting groups in the primary face of β -CD. After removal of excess NH₄F by a simple purification process, the deprotected intermediate was hydrogenolyzed with 10% Pd/C to give the desired catalyst **1** in good yield (two steps, 79%). In addition, an attempt to directly hydrogenate 5 with hydrogen gas in the presence of 10% Pd/C resulted in the deprotection of only the N-Cbz and O-Bn groups on proline residue, and thus 2 was isolated in 93% yield (Scheme 2, Cbz = benzyloxy carbamate; Bn = benzyl).

The all deprotected **1** is well soluble in water as expected, while the TBDMS-protected 2 displays poor solubility in water. We next examined the catalytic activity of the newly synthesized catalysts toward the asymmetric aldol reactions in water. Initially, the direct aldol reaction of 4-nitrobenzaldehyde (6a) and acetone was tested in the presence of 5 mol % of 1 in aqueous media (Scheme 3). Pleasingly, the reaction proceeded smoothly and complete conversion was observed within 10 h at 0 °C, and the desired aldol product 7a was isolated in 97% yield, along with a good enantiomeric excess (76% ee) as analyzed by HPLC with a chiral column. Lowering the reaction temperature to -18 °C led to a slightly higher ee value (82%), although the yield of **7a** dropped to 86% after 20 h. This result is comparable to that obtained from amide-bridging proline- β -CD conjugate catalysts as previously reported.¹² Since **1** is poorly soluble in acetone, an attempted reaction at 0 °C in neat condition without the addition of water was much sluggish, while a similar enantioselectivity was revealed. Decreasing the loading amount of acetone to 5.0 equiv gave a little lower yield but the same ee value. Therefore, the presence of water is essential to 1-catalyzed reactions by both improving the reactivity and facilitating the recycling of catalysts (vide infra). In addition, the less water-soluble catalyst 2 (5 mol %) was also tested for the reaction shown in Scheme 3, and the result showed that the reaction was much slower and only moderate ee value (52%) was observed. A controlled experiment using **2** as a catalyst in neat condition was also tested, yet the result remained in the same range. The absolute configuration of the aldol product 7 was determined to be S by comparing its optical rotation with the reported data in the literature.^{10,11}

To evaluate the substrate scope of the **1**-catalyzed aldol reactions in water, a variety of aldehydes including both aromatic and aliphatic aldehydes were employed, and the results are summarized in Table 1. The results indicate that not only aromatic aldehydes but also aliphatic aldehydes undergo the aldol condensation with acetone in moderate and good yields, and good to high enantioselectivities (up to 99% ee) were achieved in most cases. For example, the reactions involving various para-substituted benzaldehydes having electro-withdrawing groups on the benzene ring furnished the corresponding aldol adducts in high yields (entries



Scheme 2. Reagents and conditions: (a) Triphosgene, aq NaHCO₃/DCM, 0 °C-25 °C, 80%; (b) 1. NH₄F, MeOH, reflux, 97%; 2. MeOH/H₂O, 10% Pd/C, H₂, 81%. (c) MeOH, 10% Pd/C, H₂, 93%.



Scheme 3. The asymmetric aldol condensation between 4-nitrobenzaldehyde and acetone catalyzed by **1**.

Table 1

The direct asymmetric aldol reactions between various aldehydes $({\bf 6})$ and acetone catalyzed by ${\bf 1}$ in water a



Entry	Substrate	Product	T (°C)	Time (h)	Yield ^b (%)	ee ^c (%)
1	$4-NO_2C_6H_4$ (6a)	7a	-18	20	86	82
2	$4-CNC_{6}H_{4}$ (6b)	7b	0	12	>99	78
3	$4-CF_{3}C_{6}H_{4}(6c)$	7c	25	24	93	80
4	$4-ClC_{6}H_{4}(6d)$	7d	25	72	30	77
5	$4-FC_{6}H_{4}(6e)$	7e	25	72	38	79
6	C_6H_5 (6f)	7f	25	72	16	91 ^d
7	$4-MeC_{6}H_{4}(\mathbf{6g})$	7g	25	36	62	82
8	$4-MeC_{6}H_{4}(\mathbf{6g})$	7g	0	48	56	94
9	$4^{-t}BuC_{6}H_{4}(6h)$	7h	25	48	60	84
10	$4^{-t}BuC_{6}H_{4}(6h)$	7h	0	72	32	92
11	$4-MeOC_{6}H_{4}(6i)$	7i	25	72	46	76
12	cyclo-C ₆ H ₁₁ (6j)	7j	25	48	26	>99 ^d
13	<i>i</i> -Bu (6k)	7k	25	24	73	86
14	<i>t</i> -Bu (6l)	71	25	72	<5	n.d.
15	<i>n</i> -Bu (6m)	7m	25	24	80	88
16	<i>n</i> -C ₅ H ₁₁ (6n)	7n	25	16	76	91
17	$n-C_8H_{17}$ (60)	70	25	72	10	82 ^d
18	$2-NO_2C_6H_4$ (6p)	7p	25	8	95	30
19	$3-NO_2C_6H_4$ (6q)	7q	25	12	93	59
20	$3-NO_2C_6H_4$ (6q)	7q	-18	16	96	66
21	$2-ClC_{6}H_{4}(6r)$	7r	25	72	10	37
22	$2,6-Cl_2C_6H_3$ (6s)	7s	25	24	97	9

 a Conditions: aldehyde (0.1 mmol), acetone (0.1 ml), 1 (0.005 mmol. 5 mol %), and H_2O (0.1 ml).

^c Determined by HPLC analyses with chiral columns.

^d Absolute configuration is not determined.

1-3, Table 1), although the halogenated 4-fluorobenzaldehye and 4-chlorobenzaldehyde gave relatively low yields (entries 4 and 5, Table 1). The ee values for these reactions vary from 77% to 82%. The stereoselectivities of benzaldehyde and other electron-rich benzaldehydes were somewhat higher, probably due to their higher binding ability with the interior cavity of catalyst 1 (entries 6-11, Table 1). Remarkably, the ee values in these reactions were found to increase significantly from 76% to 94%, and in the cases of 4-tolualdehyde and 4-tert-butylbenzaldehyde the highest ees were found when the reactions were run at 0 $^\circ C$ (entries 7 and 10, Table 1). The isolated yields for products from these reactions were slightly lower, yet comparable to the previous results in the literature.^{11,12} Similarly, aliphatic aldehydes also proceeded well for the aldol reactions under the same conditions, offering high enantioselectivities to a range of aliphatic substrates (entries 12–17, Table 1). Interestingly, the reactivities were highly dependent on the structures of substrates. Even though the reaction with cyclohexanaldehyde provided the highest ee (>99%), the yield was not ideal in contrast to other aldol adducts (entry 12, Table 1). Unbranched aliphatic aldehydes underwent well the aldol reactions in high yields (entries 15 and 16, Table 1), but the aldehyde with a longer alkyl chain was quite unfavored (entry 17, Table 1). The branched and bulky aldehyde pivaldehyde was found to be the least reactive substrate for this reaction, whereas isobutyl

Table 2

Recycling experiments of catalyst **1** for the Aldol reaction between 4-nitrobenzaldehyde and acetone^a



Entry	Loading of 1	Time (h)	T (°C)	Yield ^b (%)	ee ^c (%)
1	3%	20	-18	93	69
2	2nd cycle	20	-18	95	68
3	3rd cycle	20	-18	94	67
4	2%	6	0	92	63
5	2nd cycle	8	0	91	69
6	3rd cycle	9	0	98	72
7	4th cycle	12	0	91	73

 a Condition: 4-nitrobenzaldehyde (0.1 mmol), acetone (0.1 ml), 1 (0.002–0.003 mmol, 2–3 mol %), and H_2O (0.1 ml).

^b Isolated yield.

^c Determined by HPLC analysis with chiral AD-H column.

aldehyde worked smoothly, affording the corresponding product in 73% yield and 86% ee (entries 13 and 14, Table 1).

To better understand the substrate selectivity of the aldol reactions, we also examined the reactions with several other substituted aromatic aldehydes other than those described above (entries 18–22, Table 1). It is worth noting that the enantioselectivities of products decreased dramatically in the order of *para*, *meta*-, and *ortho*-substituted benzaldehydes, and only 9% ee was detected when 2,6-dichlorobenzaldehyde was used, while high yield was obtained in this case. The different stereoselectivities resulting from these aromatic substrates might be attributed to their different binding abilities with the interior cavity of β -CD on catalyst **1**, consistent with the fact the binding constants between substituted aromatics and β -CD decrease from *para*, *meta*- to *ortho*-substitution.^{10b,16}

An obvious advantage of our catalytic system is the facile recyclability of the catalyst. After completion of the reaction and subsequent extraction of the product with dichloromethane the catalyst remaining in the aqueous phase can be reused for the next cycle of reaction. Several recycling experiments for the reaction between 4-nitrbenzaldehye and acetone were conducted and the results are summarized in Table 2. When 3 mol % of 1 was used instead of 5 mol %, the reaction still underwent smoothly, along with a slightly reduced ee value. Catalyst 1 has been recycled and reused for three times with almost no change in reactivity and enantioselectivity (entries 1–3, Table 2). A similar trend was observed when the loading amount of 1 was decreased to 2 mol % for the same reaction at 0 °C over four recycling experiments (entries 4–7, Table 2).

In conclusion, we have synthesized a new water-soluble β -CD tethered proline derivative by using urea as a linker. Asymmetric aldol reactions between a variety of aldehydes and acetone have been carried out by the new organocatalyst in water and the results indicated that both aromatic and aliphatic aldehydes are appropriate substrates for this reaction, giving the corresponding aldol adducts in reasonable yields and good to high enantioselectivities (76–99% ees). Thanks to its good solubility in water, the catalyst can be facilely recycled and reused several times without decreasing the reactivity and enantioselectivity.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014. 11.084.

^b Isolated yield: Low or modest yields were due to incomplete reactions.

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