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Short Communication

Novel carbohydrate-derived prolinamide as a highly efficient, recoverable catalyst for direct aldol reactions in water

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ABSTRACT

The catalytic activity of novel carbohydrate-derived prolinamide in the enantioselective aldol reactions has been examined for the first time. The organocatalyst **2b** was found to be an efficient organocatalyst for the asymmetric aldol reaction in water. This organocatalyst is applicable to the reactions of a wide range of aromatic aldehydes with cyclic and acyclic ketones in high yields (up to 98%). These reactions exhibit high *anti*/*syn* ratios (up to 99%) and excellent enantioselectivities (up to 99%). Importantly, the catalyst can be easily recovered and recycled with only a slight decrease in enantioselectivity after five cycles.

1. Introduction

The utility development of an organocatalytic enantioselective aldol reaction is an attractive research theme because asymmetric aldol reactions are one of the most important carbon–carbon bond-forming procedures in synthetic organic chemistry [1]. Since the pioneering work by List, Barbas and their co-workers that showed L-proline could act as an efficient catalyst for direct aldol reaction between acetone and aldehydes [2], a variety of proline-derivatives have been synthesized and applied for highly asymmetric aldol reactions [3]. The well reported organocatalysts are usually based on nonchiral or chiral backbones that comprise various organic moieties, including simple amines [4], phosphine [5], amine oxide [6], sulfonamide [7], amino alcohols [8], peptides [9], cinchona alkaloids [10], 1,1′-binaphthyl-2,2′-diamine [11], cyclohexane-1,2-diamine [12], and 1,2-diphenylethane-1,2-diamine [13]. In spite of significant efforts devoted to the development of highly active organocatalysts aimed at using different catalyst backbones, it has been challenging to develop more natural, efficient backbones for construction of organocatalysts [14]. Thus, the current synthetic strategy which often relies on the derivatization of the available chiral pool of the natural organic products and the natural compounds as chiral scaffolds for the design and synthesis of catalysts has received great attention so far [15].

Recently, carbohydrates have been successfully used in many enantioselective reactions and have shown their enormous potential for asymmetric transformations [16]. In 2007, Machinami and coworkers reported the enantioselective aldol reaction between acetone and 4-nitrobenzaldehyde catalyzed by minoacyl derivatives bearing glucoside moieties [17]. Zhou et al. reported that a chiral glucose-based pyrrolidine-thioureas acted as a highly efficient organocatalyst for the asymmetric Michael reaction of cyclohexanone to both aryl and alkyl nitroolefins [18]. Some sugar-based prolinamides were used as the organocatalyst in asymmetric Michael addition, which were carried out by the Peddinti group [19]. However, one of the major limitations using organocatalyst-catalyzed reactions is the high catalyst loading (15–30 mol%) generally required to complete the organic transformations. Additionally, the challenge of reusing the expensive chiral organocatalysts has been met with limited success [20].

Following our interest in carbohydrates as a source of highly efficient chiral auxiliaries [21] and ligands [22], we have recently reported that carbohydrate-derived amino alcohols **1a**–**b** (Fig. 1) as organocatalysts are very effective for enantioselective direct aldol reaction [23]. During the course of developing new water-compatible chiral organocatalysts, we discovered that catalysts (**1a** and **1b**) carrying a “free” hydroxyl group gave rise to excellent yields for the direct aldol reaction in an aqueous medium. As we know, the asymmetric direct aldol reactions, which can be performed in water, a desirable solvent with respect to environmental concerns, safety, and cost, have received remarkable attention [24,25]. We envisaged that rational incorporation of the stereocontrolling elements

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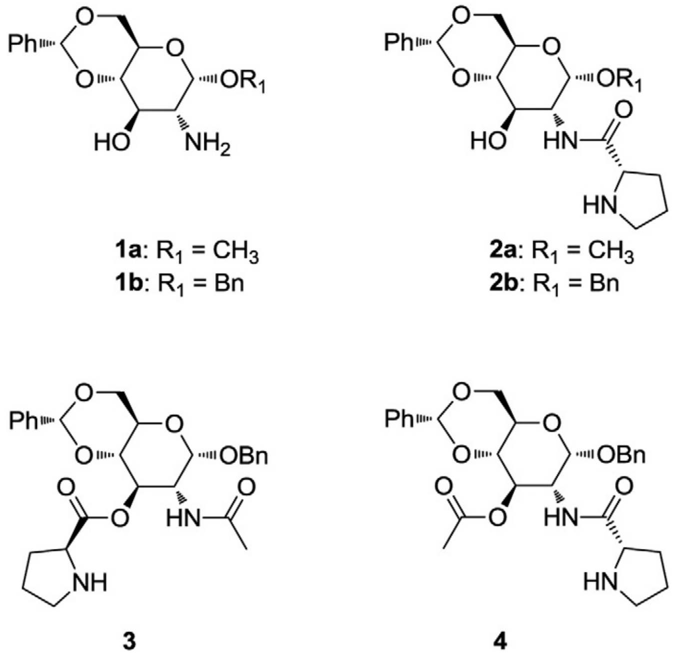


Fig. 1. Various carbohydrate-derived organocatalysts screened for aldol reaction.

of carbohydrate and proline in a single molecule would lead to a new class of chiral organocatalysts. Herein, we wish to report the systematic investigation of these green and recyclable carbohydrate-derived organocatalysts that promote aldol reactions with high levels of enantioselectivity in aqueous media.

2. Experimental

2.1. General

Solvents were commercially obtained at the highest commercial quality and were used without further purification. Column chromatography was performed on silica gel grade 60 (230–400 mesh). Analytical TLC was done with Silica Gel 60, F254 plates from Merck, which were visualized by UV and phosphomolybdic acid staining. Optical rotation values were measured on a PerkinElmer P241 polarimeter. Enantiomeric excesses (% ee) were determined by HPLC (Lab Alliance Model 500) analysis using Chiralcel OJ-H, OD or AS-H column. The ^{1}H, ^{13}C NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer; chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) are given in ppm and are referenced to residual solvent peaks (^{1}H NMR and ^{13}C NMR). Elemental analyses were performed on Carlo-Erba 1106. Compounds **1a**–**c** were prepared by previously described methods [23]. The carbohydrate-based amino alcohols **1a**–**b** were easily obtained from glucosamine through four steps [23,26]. Carbohydrate-derived organocatalysts (**2a**–**b**) were prepared by the reaction of amino alcohols with *N*-(9*H*-fluoren-9-ylmethoxy)carbony-L-proline in two steps. In these organocatalysts, each reaction center designed has a remote hydroxyl group to promote the reactivity and enantioselectivity of the molecule. To verify our hypothesis, organocatalysts (**3** and **4**) were synthesized for comparison (for details, see Supporting Information).

2.2. General experimental procedure for the aldol reactions catalyzed by **2b**

The organocatalyst **2b** (4.45 mg, 0.01 mmol), cyclohexanone (0.105 ml, 1 mmol) and benzoic acid (2.4 mg, 0.02 mmol) were stirred in 1.0 ml of water for 20 min at 0 °C. Then 4-nitrobenzaldehyde (15.1 mg, 0.1 mmol) was added and the mixture was stirred for a specified reaction time period. The mixture was treated with 10 ml of saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and concentrated to give pure aldol adduct through flash column chromatography on silica gel (hexane/ethyl acetate (3:1)). All the aldol products in the paper are known compounds that exhibited spectroscopic data identical to those reported in the literature [4].

2.3. General procedure for recycling catalyst **2b**

The organocatalyst **2b** (8.9 mg, 0.02 mmol), cyclohexanone (0.21 ml, 2 mmol) and benzoic acid (2.4 mg, 0.02 mmol) were stirred in 1.0 ml of water for 20 min at 0 °C. Then 4-nitrobenzaldehyde (30.2 mg, 0.2 mmol) was added and the mixture was stirred for a specified reaction time period. After completion of the reaction, 5 ml AcOEt was added to precipitate the catalyst **2b** as a white solid. The white product was isolated through filtration and washed with petroleum ether. The filtrate was extracted three times with petroleum ether. Then, the AcOEt/petroleum ether layers were combined and kept at 0–5 °C to result in a second crop of solid. The recovered **2b** without further purification retained essentially its catalytic activity, and only slightly a decrease of enantioselectivity was observed for five cycles.

3. Results and discussion

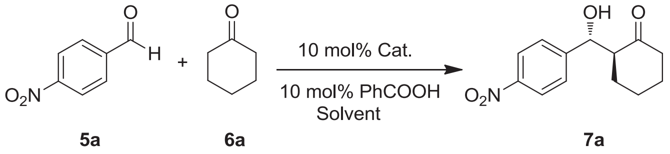
3.1. Catalytic activities of carbohydrate-derived organocatalysts in enantioselective aldol reactions

With these organocatalysts in hand, we then examined their efficiency in enantioselective aldol reaction with cyclohexanone (**6a**) and 4-nitrobenzaldehyde (**5a**) as the model substrates. The representative results were compiled in Table 1. When 10 mol% of amino alcohols **1a** and **1b** were used as the catalyst, good yields with moderate enantioselectivities were obtained at room temperature without acidic additive and all products were obtained for the major anti isomer *anti*-**7a** (entries 1 and 2, Table 1). After L-proline was introduced into the amino-group of amino alcohol, the prolinamide-modified catalysts **2a**–**b** resulted in increased reaction yields and substantially higher enantioselectivities (entries 3 and 4, Table 1). In contrast, when L-proline was introduced into the hydroxyl group of sugar moiety, catalyst **3** catalyzed the aldol condensation in lower yield and enantioselectivity, giving the product with opposite configuration with 68% yield and 56% ee (entry 5, Table 1). To search the effect of hydroxyl group on glucoside bearing structure, 3-*O* protected benzyl α-D-glucopyranoside **4** was prepared as the catalyst and applied to the aldol reaction. The catalytic reaction showed a comparative reaction efficiency, but led to a lower diastereoselectivity and enantioselectivity under the standard reaction conditions (entry 6, Table 1). We further examined the effect of solvent for the aldolization of cyclohexanone through use of catalyst **2b**.

As shown in Table 1, all attempted aldol reactions of cyclohexanone with **5a** were efficiently catalyzed by **2b**, affording the aldol adducts in good to excellent yields with high enantioselectivities (entries 8–10, Table 1). Notably, the best result was obtained by decreasing the reaction temperature to 0 °C (entry 9, Table 1). We also found that the acidic additive has a marked effect on the catalytic activity and selectivity (entry 10, Table 1).

In order to test the substrate generality of this organocatalyzed direct aldol reaction, the reactions of various aromatic aldehydes with cyclohexanone were studied under the optimized conditions. The results are summarized in Table 2. As shown in Table 2, the aldehydes substituted by a nitro group at the meta- or ortho-position (**5b** and **5c**) gave excellent yields of the corresponding *anti*-aldol products with 96% ee and 97% ee, respectively (entry 1 and 2). The reaction of the 4-cyanobenzaldehyde **5d** was carried out to afford the aldol product **7d** in good yield with 92% ee (entry 3). Similarly, halogenated

Table 1
Reaction condition optimization.[a]



Entry	Catalyst	Solvent	T [°C]	Time [h]	Yield [%][b]	*Anti*/*syn*[c]	ee [%][d]
1	**1a**	H_2O	r.t.	12	85	75:25	51[e]
2	**1b**	H_2O	r.t.	12	91	91:9	33[e]
3	**2a**	H_2O	r.t.	6	92	83:17	86
4	**2b**	H_2O	r.t.	6	95	94:6	90
5	**3**	H_2O	r.t.	24	68	90:10	−56
6	**4**	H_2O	r.t.	12	93	88:12	62
7	**2b**	Neat	r.t.	6	98	90:10	85
8	**2b**	Brine	r.t.	6	95	92:8	88
9	**2b**	H_2O	0	12	95	98:2	92
10	**2b**	H_2O	0	12	86	91:9	80[e]

[a] Reaction conditions: 1.0 mmol of **6a**, 0.1 mmol of **5a**, 10 mol% of benzoic acid and 10 mol% amount of catalyst in the specified solvent (0.5 ml).
[b] Isolated yields.
[c] Determined by ^1H NMR.
[d] Determined by HPLC on a chiral column.
[e] Without acidic additive.

benzaldehydes proceed smoothly in excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to 99%) to furnish the aldol adducts **7e**–**g** (entries 4–6). The reaction of less reactive benzaldehyde **5h** with cyclohexanone also gave **7h** with 94% ee (entry 7) while aromatic aldehydes with electron-donating groups led to comparatively lower yields and enantioselectivities (entries 8–10). Moreover, other aromatic aldehydes, such as 1-naphthaldehydes and 2-thenaldehydes, gave the expected aldol product with 91% ee and 85% ee, respectively (entry 11 and 12).

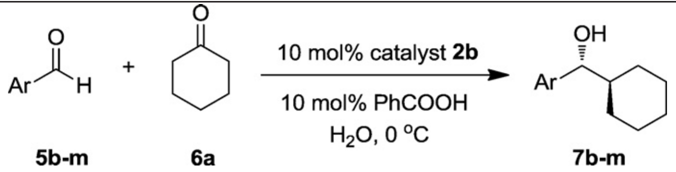
In addition, we have also preliminarily examined the feasibility of using other cyclic and acyclic ketones as aldol donors using **2b** as the catalyst. Cyclopentanone yielded *anti*-aldol products with ee value of 82% (upper equation, Fig. 2).

The reaction of 4-nitrobenzaldehyde with butanone was also investigated (lower equation, Fig. 2) to examine the scope of the aldol donors. Significantly, the reaction mainly occurred at the C-3 position to afford the *anti*-aldol products in remarkably high diastereoselectivity (89:11) and enantioselectivity (89% ee) and no other enantioselective regioisomer was observed.

3.2. Recycling and reuse of catalyst **2b**

Finally, in order to verify that the catalyst **2b** could be recovered and reused [27,28], we performed a recycling study of **2b** using the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. Enantioselectivity was observed for five cycles (Table 3). After completion of the reaction, the catalyst **2b** could be easily recovered from the reaction mixture by adding AcOEt, filtration, washing with petroleum ether and directly used it in subsequent aldol reaction without adding any new catalyst. In each reuse, the same amounts of substrates were used, and the recovered

Table 2
Catalytic asymmetric aldol reactions of ketones with aromatic aldehydes.[a]



Entry	Ar	Time [h]	Yield [%][b]	*Anti*/*syn*[c]	ee [%][d]
1	3-$NO_2C_6H_4$	12	92	97:3	96
2	2-$NO_2C_6H_4$	12	99	92:8	97
3	4-CNC_6H_4	24	85	95:5	92
4	4-FC_6H_4	48	82	85:15	90
5	4-ClC_6H_4	48	86	94:6	99
6	4-BrC_6H_4	48	80	99:1	98
7	Ph	72	62	75:25	94
8	4-$MeOC_6H_4$	144	73	77:23	86
9	3-MeC_6H_4	144	71	92:8	88
10	2-$MeOC_6H_4$	144	66	88:12	88
11	1-Naphthyl	72	73	94:6	91
12	2-Thienyl	72	76	89:11	85

[a] Reaction conditions: 1.0 mmol of **6a**, 0.1 mmol of aldehyde, 10 mol% of benzoic acid and 10 mol% amount of catalyst in 0.5 ml of H_2O, 0 °C.
[b] Isolated yields.
[c] Determined by ^1H NMR.
[d] Determined by HPLC on a chiral column.

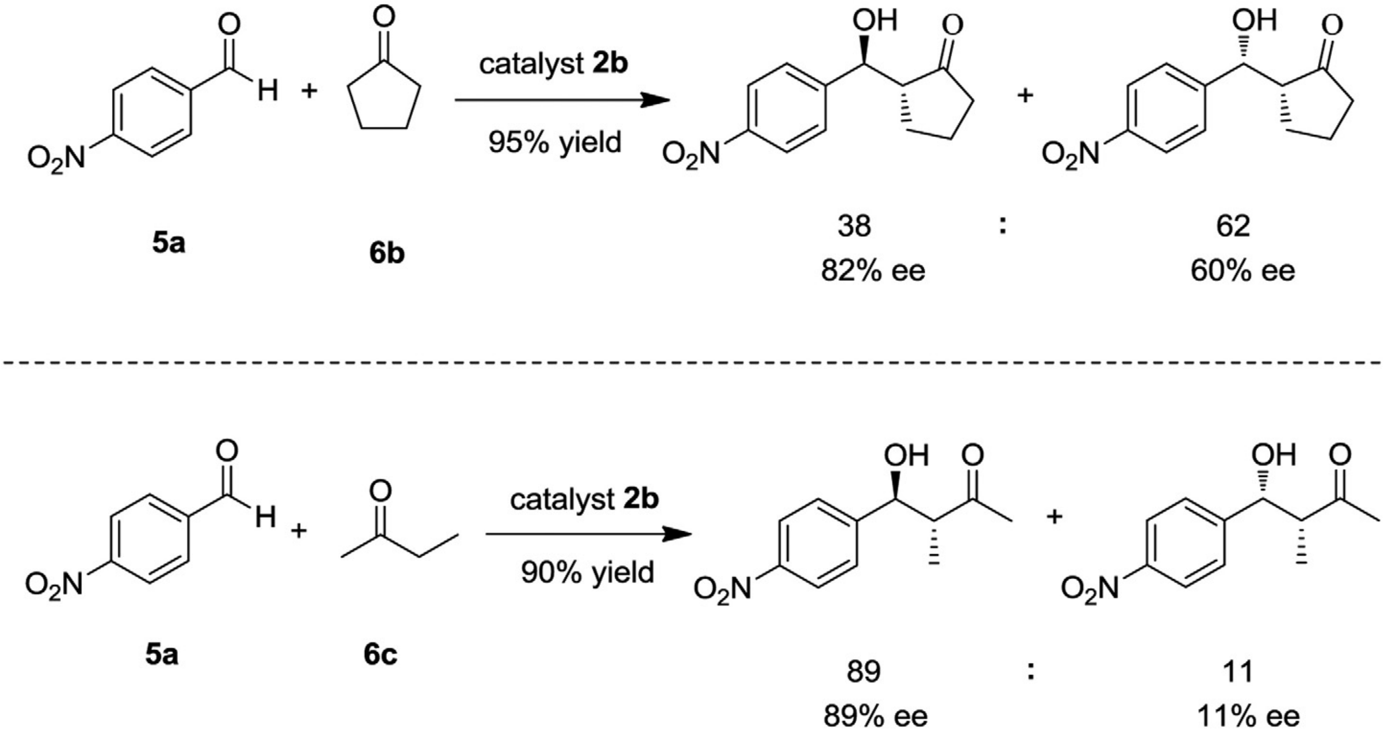


Fig. 2. Exploration of substrate scope with catalyst **2b**.

2b without further purification, essentially retained its catalytic activity, and only slightly a decrease in enantioselectivity was observed after five cycles (Table 3).

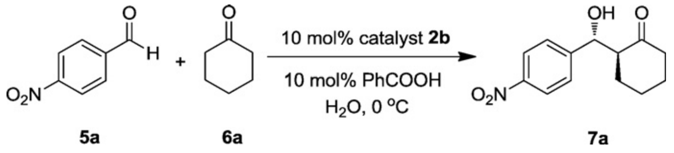
3.3. The mechanism for the asymmetric induction with organocatalyst **2b**

Therefore, we suppose that the carbohydrate-derived organocatalyst **2b**-catalyzed direct aldol reactions between aldehydes and ketones proceed via a transition state proposed by Gong et al. [14]. Based on the stereochemistry of aldol products **7**, we guess that the hydroxy group and prolinamide coordinate to aldehydes and stabilize the transition state (Fig. 3). First, the proline may be readily manipulated in configuration to allow rapid fine-tuning of their function. Then the enamines react with the incoming aldehyde, likely activated by the NH and OH of the catalyst in intermediates, according as the major products the corresponding *anti*-aldol adducts, so that the catalytic activity and enantioselectivity might be enhanced.

4. Conclusion

In conclusion, we have developed a new type of carbohydrate-derived prolinamide organocatalysts, which is capable of catalyzing asymmetric aldol reaction, a remarkably better catalytic performance was provided by the reactions in terms of productivity (up to 98%), diastereoselectivity (*anti*/*syn* 99:1), enantioselectivity (up to 99%) in water. The simple and environmentally friendly experimental procedure and the recycling of the catalytic system highlight good assets of this catalytic protocol. Further investigations on the application of this kind of organocatalyst in asymmetric catalysis are still underway in our laboratory.

Table 3
Recycling and reuse of catalyst **2b**.[a]



Entry	Time [h]	Yield [%][b]	*Anti*/*syn*[c]	ee [%][d]
1	12	95	98:2	92
2	12	93	94:6	92
3	24	85	95:5	91
4	24	80	95:5	90
5	36r	75	92:8	90

[a] Reaction conditions: 2.0 mmol of **6a**, 0.2 mmol of **5a**, 10 mol% of benzoic acid and 10 mol% amount of catalyst **2b** in 1.0 ml H_2O (without additional **2b** for next cycle), 0 °C.
[b] Isolated yields.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC (Chiracel OD).

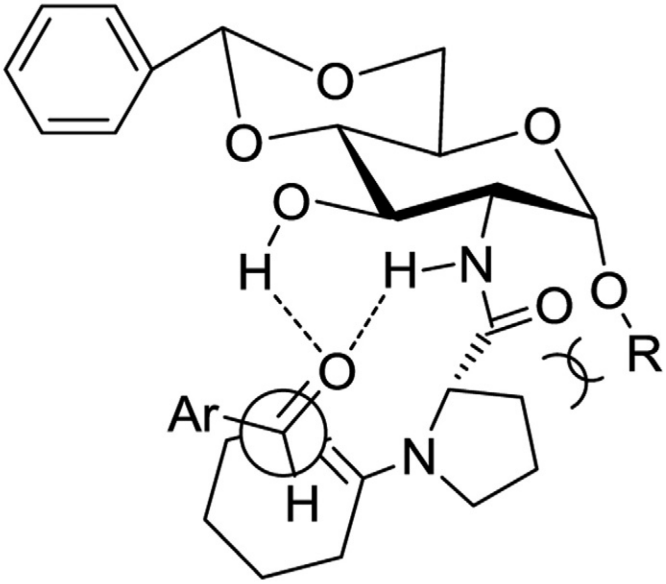


Fig. 3. Transition states for aqueous aldol reactions.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2012.05.004.

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