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Short Communication

Novel synthesis of carbohydrate-derived organocatalysts and their application in asymmetric aldol reactions ☆

Chao Shen [a], Hanxiao Liao [b], Fangyi Shen [b], Pengfei Zhang [b,*]

[a] College of Biology and Environmental Engineering, Zhejiang Shuren University, Hangzhou 310015, China
[b] College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, PR China

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ABSTRACT

Carbohydrate as a kind of important chiral scaffold is widely recognized for its obvious advantages cheap and readily available. A new type of prolinamide organocatalysts, derived from carbohydrate, was synthesized in high yield, and the novel organocatalysts were applied to the direct asymmetric aldol reactions of cyclohexanone and various aromatic aldehydes. The corresponding aldol products were obtained in high yields (up to 99%) with excellent diastereoselectivities (up to >98:2 dr) and enantioselectivities (up to 97% ee) under mild reaction conditions.

1. Introduction

Organocatalysis has seen a tremendous rise in popularity when measured in publications and hence in references [1,2]. This might indicate that a gap between metal- and enzyme-catalysis existed, which now is being filled by organocatalysis, offering highly stereoselective transformations of versatile starting materials, using easy procedures, although at the expense of generally high catalytic loadings. One of the main advantages of asymmetric catalysis over other methods is that products can be selectively synthesized from cheap prochiral starting materials without undesirable products being formed [3]. A lot of these chiral catalysts are usually based on chiral backbones that comprise various organic moieties, such as chiral amino alcohol, cinchona alkaloids, diamine, prolinamides and their derivatives [4–7]. Despite significant efforts devoted to the development of highly active catalysts aimed at using different catalyst backbones, it has been challenging to develop more natural, efficient backbones for construction of chiral catalysts [8]. Thus, the current synthetic strategy 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 have received great attention so far [9].

Asymmetric aldol reaction is one of the most important organocatalytic C-C bond-forming reactions [10,11]. It can be efficiently carried out in the presence of various organocatalysts; among them, prolinamide-derived organocatalysts generally show good catalytic performance [12–18]. In recent years, asymmetric reactions catalyzed by the carbohydrate-based catalysts are the intensively studied as they have been recognized as versatile starting materials for chiral auxiliaries, reagents, ligands and organocatalysts [19–22]. The design and fine-tuning of carbohydrate-based catalysts is facilitated by the multiple functional groups present within this class of compounds. This strategy has provided unique ligand moieties which combine the performance of "privileged catalysts" with increased flexibility and accessibility. In 2007, the first examples of carbohydrate-derived urea and thiourea organocatalysts have appeared in the literature. Bifunctional urea Schiff base organocatalysts were reported by Becker et al. [23].In the Strecker reaction of aldimine with trimethylsilyl cyanide, the organocatalysts yielded product in good ee. In 2010, our research group described the first application of D-glucosamine-derived amino alcohols as organocatalysts in the enantioselective aldol reactions of cyclohexanone with isatin and its derivatives. A variety of isatins were used as substrates, and the corresponding aldol products were obtained in excellent chemical yields with high yields (up to >99%) and moderate enantioselectivity (up to 75% ee) [24]. Recently, we have developed a new type of carbohydrate-derived prolinamide organocatalyst, which is capable of catalyzing asymmetric aldol reaction, and a remarkably better catalytic performance was provided by the reactions in terms of productivity (up to 98%), diastereoselectivity (anti/syn 99:1) and enantioselectivity (up to 99%) in water [25]. Independently and almost simultaneously, Pedatella and coworkers [26]reported a new synthetic catalyst, which were prepared by O-TBDPS D-glucosamine coupled with L-proline, acting as an efficient organocatalyst in the accomplishment of direct aldol reactions. Good chemical yields, as well as

* Corresponding author. Tel./fax: +86 571 28862867.
E-mail address: chxyzpf@hotmail.com (P. Zhang).

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diastereomeric and enantiomeric ratios, were reported for the catalyzed additions of cyclohexanone and acetone to variously substituted benzaldehydes [27].

As part of our continued interest in the development of new organocatalysts [24,25], herein we would like to introduce a new kind of organocatalysts that combined carbohydrate with prolinamide to be as a new organocatalysts and the study of its application in aldol reaction between cyclohexanone and substituted benzaldehydes.

2. Experimental

2.1. Materials and methods

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: 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 and ^{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 parts per million and are referenced to residual solvent peaks (^{1}H NMR and ^{13}C NMR). Elemental analyses were performed on Carlo-Erba 1106.

2.2. Procedure for the synthesis of compound 1–3

The synthesis of compounds **1–3** was carried out according to the literature procedure and our previous work [28,29].

2.3. Procedure for the synthesis of compound 4

Firstly, to a stirred solution of 20 mL THF, 0.31 mL Et_3N and 0.674 g (2 mmol) *N*-(9H-fluoren-9-yl)methoxy)carbony-L-proline, 0.21 mL ethyl carbonochloridate was added to at 0 °C, the reaction mixture was stirred at 0 °C for 30 minutes and compound **3** (2 mmol) was added then stirred at room temperature for 16 h and heated at reflux for 3 h, the reaction was continually monitored by TLC analysis. At the end of the reaction, the organic phase was evaporated under reduced pressure to give the crude product. For the deprotection of the Fmoc-protected prolinamide derivative, piperidine (0.56 mL, 5.64 mmol) was added to a 0 °C solution of mixture (1.56 mmol) in CH_3CN (30 mL). The resulting mixture was maintained at 0 °C for 30 min and at room temperature for 3 h, and the reaction was continually monitored by TLC analysis then concentrated. The residue was further purified by column chromatography on silica gel to give final organocatalyst **4**.

2.4. Procedure for the synthesis of organocatalyst 5

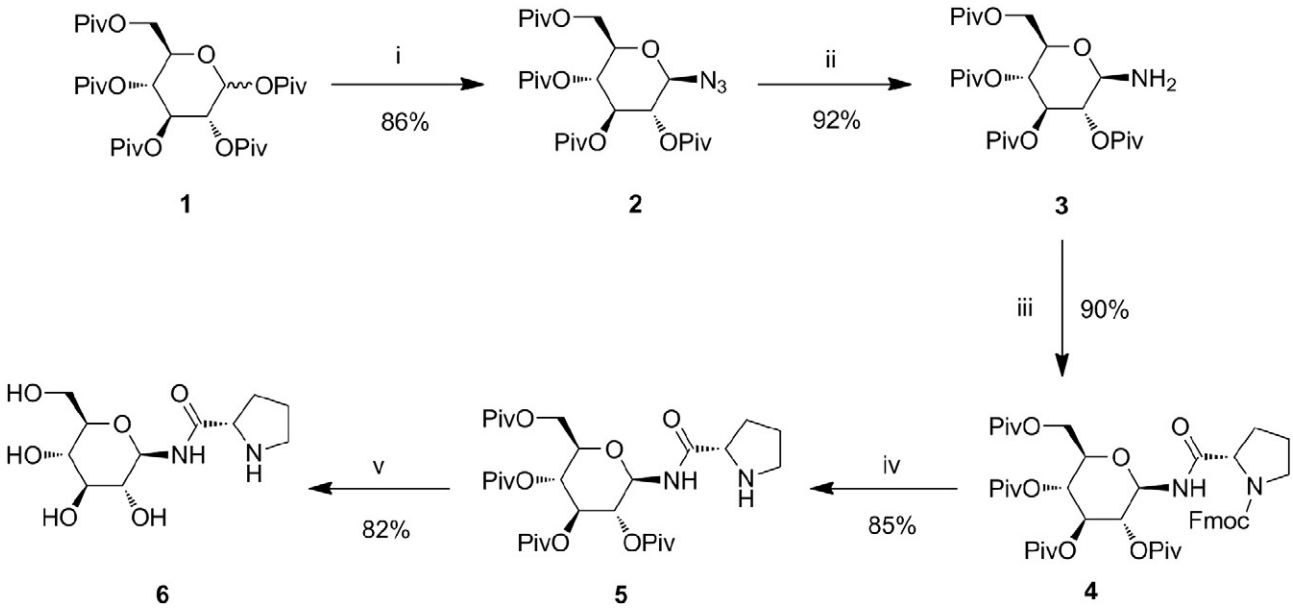
Piperidine (0.56 mL, 5.64 mmol) was added to a 0 °C solution of Fmoc **4** (2.82 mmol) in CH_3CN (30 mL). The resulting mixture was maintained at 0 °C for 30 min and at room temperature for 3 h and then concentrated. The crude residue was purified by recrystallization from EtOH to give pure white solid **5.**

2.5. Procedure for the synthesis of organocatalyst 6

Compound **5** (1 mmol) was dissolved in 10 mL 5 N $NaOCH_3$/CH_3OH solution and the reaction was monitored by TLC (10:1 ethyl acetate/CH_3OH). Upon completion, 2 N HCl was added until the solution was at neutral pH and was filtered. The solution was concentrated in vacuo and purified by flash chromatography 10:1 ethyl acetate/CH_3OH to give white product.

2.6. Representative procedure for the organocatalytic asymmetric aldol reaction

The organocatalyst (0.005 mmol), cyclohexanone (0.105 ml, 1 mmol) and benzoic acid (2.4 mg, 0.02 mmol) was stirred in 1.0 mL of DMSO water for 20 min at 0 °C. Then aromatic aldehydes (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. The anti:syn ratio was determined by 400 MHz ^{1}H NMR. The *anti* ee was determined by HPLC on chiral



Scheme 1. Synthesis of novel carbohydrate-derived organocatalysts **5**–**6**.

column (Daicel, Chiralpak, OD or AD). All the experiments were duplicated.

3. Results and discussion

With these organocatalysts in hand (Scheme 1), we then examined their efficiency in enantioselective aldol reaction with 4-nitrobenzaldehyde (**7a**) and cyclohexanone (**8**) as the model substrates. Initially, we screened the new catalysts in catalyzing the direct aldol reaction, respectively, in water with acidic additive at room temperature for 12 h, and the results were summarized in Table 1.

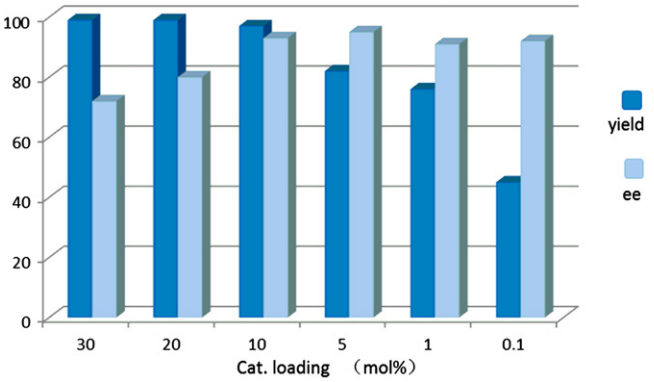
We can find that 10 mol% of catalyst **5** show activity with good ee and moderate yield (Table 1, entry 1). Good yield and moderate ee value was reached when catalyst **6** was adopted (Table 1. entry 2). Then optimization of the reaction conditions focusing on the effect of the solvent (Table 1, entries 3–8) revealed that the mixture of (1:1) (DMSO/water) is the best solvent leading to the quantitative conversion of the substrate in a shorter time and afforded the product with 96% yield and 90% ee (Table 1, entry 8).

We further examined the effect of temperature for the aldolization of cyclohexanone through use of catalyst **5**. The best result was obtained by decreasing the reaction temperature to 0 °C (Table 1, entry 9). When decreasing the reaction temperature to −25 °C, product **9a** was obtained with 92% ee, but the reaction was sluggish (Table 1, entry 10). Based on this cognition, we take 0 °C as the best temperature in this reactions.

Further, we varied catalyst loading to see its influence on the reaction. When the catalyst loading was varied, we can find that it did really influence the rate and the ee value of the reaction (Fig. 1). For example, when the reaction was performed by using 30 mol% organocatalyst **5**, the reaction was completed in good yield but with low ee value. However, when less catalyst was involved, for example 5 mol%, a lower yield but higher ee value was obtained. Likewise, if less catalyst was taken, for example, 1 mol% or 0.1 mol%, both the yield and the ee values would be decreased. Based on the results in Fig. 1, we chose catalyst **5** at 5 mol % loading for further study.

With the optimized reaction parameters in hand, the substrate scope of enantioselective aldol reaction of cyclohexanone with other aromatic aldehydes was further investigated. The nitro, chloro and cyano substituents were chosen as electron-withdrawing groups, and the methoxy and methyl substituent as a representative electron-donating group. As shown in Table 2, the aldehydes substituted by a nitro group at the *ortho*- and *meta*-position gave good yields of the corresponding aldol products with 96% ee and 96% ee (Table 2, entries 2–3). Similarly, chloro and cyano substituents proceed smoothly in excellent enantioselectivities to furnish the aldol adducts **9d** and **9e** (Table 2, entries 3–4). The reaction of less reactive benzaldehyde **7h, 7i** and **7i** with cyclohexanone also gave products with 90% ee, 88% ee and 91% ee, respectively (Table 2, entries 6–8). The reaction between acetone and 4-nitrobenzaldehyde was also carried out in the presence of catalyst **5**. However, the asymmetric induction was not impressive. The reaction was performed at 0 °C to produce the aldol product in 52% ee only.

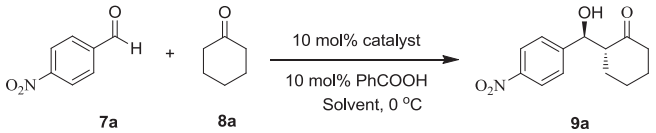
In conclusion, we have reported the novel synthesis of carbohydrate-derived prolinamide organocatalysts, which is capable of catalyzing asymmetric aldol reaction. We screened out the catalyst, solvent, temperature and catalyst loading. The products of the reaction between cyclohexanone and aromatic aldehydes were obtained in high yields (up to 99%) with excellent diastereo (up to >98:2 dr)- and enantioselectivities (up to 97% ee). Further investigations on the application of this kind of organocatalysts in asymmetric catalysis are still under way in our laboratory.



[a] Reaction conditions: 0.1 mmol of **7a**, 1.0 mmol of **8**, 10 mol% or 1 mol% of carbohydrate-derived organocatalysts in neat.

Fig. 1. Optimization catalyst loading for the aldol reaction.[a]

Table 1
Optimization condition for the aldol reaction.[a]

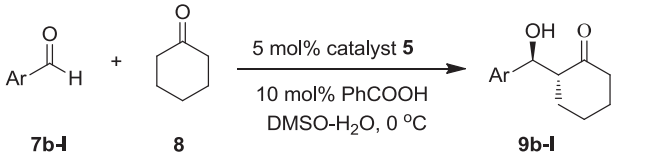


7a 8a 9a

Entry	Catalyst	Solvent	*T* (°C)	Time (h)	Yield (%)[b]	Anti/syn[c]	ee (%)[c]
1	**5**	H_2O	rt	12	65	95:5	85
2	**6**	H_2O	rt	12	82	85:15	76
3	**5**	Brine	rt	12	72	90:10	83
4	**5**	neat	rt	12	96	92:8	81
5	**5**	$PhCH_3$	rt	12	90	93:7	79
6	**5**	CH_2Cl_2	rt	12	92	88:12	82
7	**5**	DMSO	rt	12	93	95:5	88
8	**5**	DMSO/H_2O	rt	12	96	94:6	90[d]
9	**5**	DMSO/H_2O	0	**12**	97	**98:2**	93[d]
10	**5**	DMSO/H_2O	−25	24	51	96:4	92[d]
11	**5**	DMSO/H_2O	0	24	81	92:8	84[d,e]
12	**6**	DMSO/H_2O	0	24	86	95:5	77 [d]

[a] Reaction conditions: 0.1 mmol of **7a**, 1.0 mmol of **8**, 10 mol% **5** or **6** and 10 mol% benzoic acid was added as additive.
[b] Isolated yields.
[c] Determined by HPLC on a chiral column.
[d] The mixture of (1:1)(DMSO/water) was employed as a solvent.
[e] Without benzoic acid.

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



7b-l 8 9b-l

Entry	Ar+	Time (h)	Yield (%)[b]	Anti/syn[c]	ee (%)[c]
1	3-$NO_2C_6H_4$ (**b**)	24	99	95:5	96
2	2-$NO_2C_6H_4$ (**c**)	24	96	97:3	97
3	4-CNC_6H_4 (**d**)	24	90	97:3	95
4	4-ClC_6H_4 (**e**)	24	95	92:8	97
5	Ph (**f**)	24	86	91:9	96
6	4-$MeOC_6H_4$ (**g**)	48	87	95:5	90
7	3-MeC_6H_4 (h)	48	82	93:7	88
8	2-$MeOC_6H_4$ (**i**)	48	86	96:4	91

[a] Reaction conditions: 0.1 mmol of **7**, 1.0 mmol of **8**, 5 mol% **5** and 10 mol% benzoic acid in 1.0 mL of DMSO/water at 0 °C.
[b] Isolated yields.
[c] Determined by HPLC on a chiral column.

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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.2013.07.011.

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