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Highly efficient and solvent-free direct aldol reaction catalyzed by glucosamine-derived prolinamide

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ABSTRACT

The catalytic activity of novel sugar-based prolinamides in the aldol reaction between ketones and aryl aldehydes has been examined. The prolinamide **1c** was found to be an efficient organocatalyst for the asymmetric aldol reaction under solvent-free conditions. A variety of ketones and aldehydes were used as substrates and the corresponding aldol products were obtained in excellent chemical yields with high levels of *anti* diastereoselectivity (up to 99:1) and enantioselectivity (up to >99%).

1. Introduction

Asymmetric organocatalysis has attracted a great deal of attention by scientists worldwide due to its wide applicability in various organic transformations.[1–3] After the pioneering work reported by List, Barbas and Lerner which proves proline as an active and versatile organocatalyst in the asymmetric aldol reaction,[4] numerous organocatalysts have been designed for this reaction. In recent years, prolinamides have been established as another class of organocatalysts for the direct asymmetric aldol reaction.[5,6] Although the introduction of an amide linkage provides more opportunity to perform reactions in various organic solvents, some drawbacks such as longer reaction times and low selectivities are associated with prolinamide catalysis.

To the best of our knowledge, only one report is published using sugar-based prolinamides as organocatalyst.[7] Machinami et al. have employed methyl 2-deoxy-2-(L-prolyl)amido-α-D-glucopyranoside as an organocatalyst for the direct asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde in water as a solvent and they obtained the corresponding aldol adduct in moderate yield and enantioselectivity. The generality of this sugar-based organocatalyst is not known and the improvement of both yield and asymmetric induction for the reported example is still required.

Our laboratory has taken a long-term goal of developing novel chiral catalysts for asymmetric synthesis.[8] In this context, we have developed a sugar-based prolinamide bearing two stereogenic structural motifs in the same molecule with an amide linkage (Fig. 1). We reasoned that hydrogen bonding between the amide proton and carbonyl group of the aldehyde and effective blocking of one face of the aldehyde with the substituted sugar moiety bearing an α-alkyloxy group at the anomeric position would result in an asymmetric induction. At the same time the presence of benzyl groups on the sugar moiety improves its solubility in the reaction medium which may lead to an enhancement in the rate of reaction.

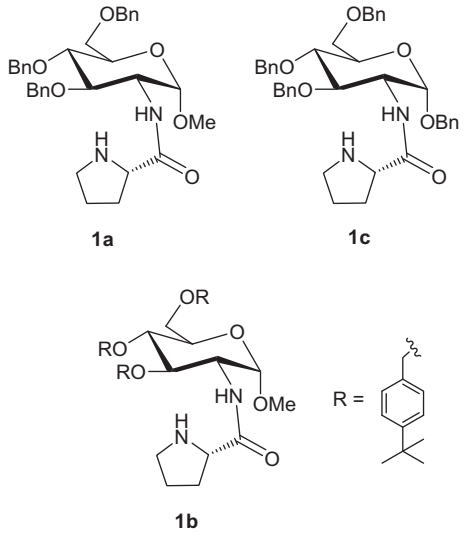

Figure 1. Structures of sugar-based prolinamides.

2. Results and discussion

Herein we report sugar-based novel prolinamide-catalyzed highly diastereoselective and enantioselective aldol reactions in solvent-free conditions. Initially, we investigated the direct

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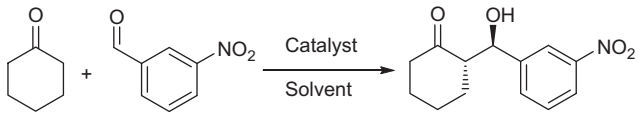
intermolecular aldol reaction between 3-nitrobenzaldehyde **2b** and cyclohexanone using catalyst **1a**. Several polar and nonpolar solvents have been screened at room temperature. To our surprise, the best results were obtained in neat conditions when the reaction was performed with 15 equiv of ketone. The reaction was completed within 3 h with an excellent chemical yield and a good enantioselectivity (Table 1, entry 7). To improve the enantiomeric excess of the reaction, the benzyl groups of the catalyst **1b** were replaced with bulky *p*-*tert*-butylbenzyl groups. However, no improvement in enantioselectivity was observed (Table 1, entry 9). At this juncture, the anomeric methoxy group of **1a** was replaced with a benzyloxy group and the aldol reaction was carried out between cyclohexanone and 3-nitrobenzaldehyde at room temperature. Gratifyingly, the prolinamide **1c**-catalyzed aldol reaction provided the adduct **3b** with an excellent chemical yield and high enantioselectivity. The asymmetric induction was further improved by conducting the reaction at 0 °C under neat conditions using 20 mol % catalyst loading (Table 1, entry 12).

Table 1
Optimization conditions for the aldol reaction[a]



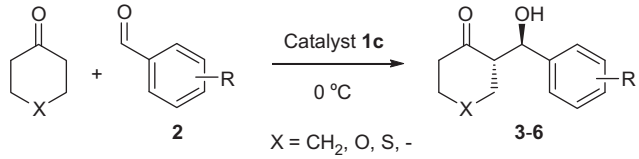
2b **3b**

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)	
					anti:*syn*	*anti*:	*syn*
1	**1a**	MeOH	96	90	65:35	27	23
2	**1a**	CH_2Cl_2	96	94	67:33	46	38
3	**1a**	$CHCl_3$	96	90	70:30	43	33
4	**1a**	DMSO	96	82	58:42	61	12
5	**1a**	H_2O	7	95	54:46	27	22
6	**1a**	DMSO/H_2O 4:1	96	92	60:40	30	24
7	**1a**	Neat	3	98	80:20	69	26
8[e]	**1a**	Neat	7	97	90:10	72	—
9	**1b**	Neat	4	91	82:18	68	—
10[e]	**1b**	Neat	7	89	91:9	74	—
11	**1c**	Neat	3	97	90:10	88	—
12[e]	**1c**	Neat	5	96	91:9	93	—

[a] Reactions were performed with cyclohexanone (0.4 mM) and 3-nitrobenzaldehyde (0.2 mM) in the presence of organocatalyst **1** (0.04 mM) in 0.5 mL of solvent in entries 1–6; cyclohexanone (0.3 mL) and 3-nitrobenzaldehyde (0.2 mM) were used in entries 7–12.
[b] Pure and column chromatographically isolated yields.
[c] Determined by ^{1}H NMR of the crude sample.
[d] Determined by HPLC analysis (Chiralpak OD-H).
[e] Reaction was performed at 0 °C.

To evaluate the substrate scope for this reaction, several aromatic aldehydes with diversified substituents were tested in the presence of 20 mol % organocatalyst **1c**. Numerous electron-rich and electron-deficient aldehydes with different substitution patterns gave rise to products **3a**–**l** in high yields and with high levels of diastereo- and enantioselectivity (Table 2). In all cases, *anti* aldol products were obtained with high enantioselectivity and diastereoslectivity and the rate of reactions depends upon the position and nature of the substitution on the aromatic moiety. The reactions of cyclohexanone with nitrobenzaldehydes were faster irrespective of the position of the nitro functionality and afforded the corresponding aldol adducts **3a**–**c** in good diastereoselectivity and enantioselectivity (Table 2, entries 1–3). The halo-benzaldehydes participated in the aldol reaction to provide

Table 2
Aldol reaction of cyclic ketones with substituted benzaldehydes in the presence of **1c**[a]



2 **3-6**

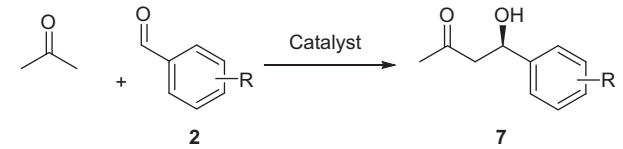
S. No.	X	R	Product	Time (h)	Yield[b] (%)	anti:syn[c]	ee[d] (%)
1	CH_2	*o*-NO_2	**3a**	5	97	97:3	96
2	CH_2	*m*-NO_2	**3b**	5	96	91:9	93
3	CH_2	*p*-NO_2	**3c**	5	98	93:7	91
4	CH_2	*o*-Br	**3d**	21	85	97:3	97
5	CH_2	*p*-Br	**3e**	16	89	91:9	97
6	CH_2	*o*-Cl	**3f**	20	91	98:2	96
7	CH_2	*p*-Cl	**3g**	20	82	91:9	>99
8	CH_2	*p*-CN	**3h**	10	97	90:10	91
9	CH_2	*p*-F	**3i**	9	99	71:29	94
10	CH_2	*1-Naphthyl*	**3j**	21	91	99:1	99
11	CH_2	*o*-OMe	**3k**	25	86	97:3	99
12	CH_2	*p*-OMe	**3l**	26	87	77:23	98
13	O	*o*-NO_2	**4a**	7	96	94:6	97
14	O	*p*-NO_2	**4b**	6	95	95:5	84
15[e]	S	*o*-NO_2	**5a**	48	89	98:2	97
16[e]	S	*p*-NO_2	**5b**	48	92	94:6	95
17	—	*o*-NO_2	**6a**	7	98	48:52	>99 (82)[f]
18	—	*m*-NO_2	**6b**	8	94	28:72	89 (86)[f]
19	—	*p*-NO_2	**6c**	7	98	18:82	86 (85)[f]
20	—	*o*-Br	**6d**	16	89	51:49	83 (94)[f]
21	—	*p*-Br	**6e**	16	87	38:62	>99 (83)[f]

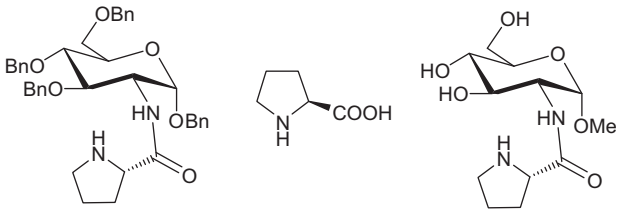
[a] Reactions were performed with cyclic ketone (0.3 mL) and an aryl aldehyde (0.2 mM) in the presence of organocatalyst **1c**.
[b] Pure and column chromatographically isolated yields.
[c] Determined by ^{1}H NMR of the crude sample.
[d] Ee of anti products determined by HPLC analysis.
[e] Reaction was performed with ketone (0.4 mM) and aryl aldehyde (0.2 mM) in the presence of organocatalyst **1c** in 0.5 mL of CH_2Cl_2.
[f] In parenthesis, ee of *syn* product is given.

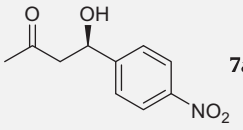
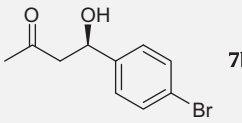
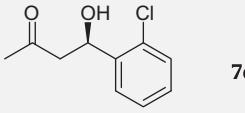
adducts **3d**–**g** with excellent enantioselectivities (Table 2, entries 4–7). The reaction of 4-fluorobenzaldehyde was relatively faster than those of other halo-benzaldehydes, and the fluoro-adduct **3i** was obtained in excellent enantiomeric excess with diminished diastereoselectivity (Table 2, entry 9). The product **3h** with *p*-cyano-substitution was obtained in comparable selectivities as those of aldol adduct **3c** bearing *p*-nitro-substitution. It is worth mentioning here that though the reactions of 1-naphthyl aldehyde and methoxybenzaldehydes were slow, the corresponding adducts **3j**–**l** were obtained in almost enantiomerically pure form (Table 2, entries 10–12). Other cyclic ketones such as tetrahydropyran-4-one and tetrahydrothiopyran-4-one have also been used as aldol donors. These reactions afforded the products **4** and **5** in high to excellent diastereoselectivities and enantioselectivities. We observed that the reaction times are significantly increased in instances where the reactions are performed in solvent for the solid ketone tetrahydrothiopyran-4-one (Table 2, entries 15 and 16).

Encouraged by the results obtained with six-membered cyclic ketones, we next probed the aldol reaction between aryl aldehydes and cyclopentanone using catalyst **1c**. The results are summarized in Table 2. Although the diastereoselectivities are not impressive, both the *syn* and *anti* products were obtained in very high enantioselectivities. The acyclic ketone acetone also worked well in the reactions with the tested aromatic aldehydes. These reactions afforded the desired aldol products **7a**–**c** in 7–14 h in high yields with no dehydration products being isolated. The asymmetric induction in these reactions is better in comparison with those catalyzed by proline **8**[4a] or sugar-based prolinamide **9**[7] (Table 3).

Table 3
Aldol reaction of acetone with substituted benzaldehydes[a]





Entry	Catalyst (mol %)	Product	Solvent	Yield (%)	ee (%)
1	**1c** (20)	 **7a**	—	98	95
2	**8** (30)		DMSO	68	76
3	**9** (30)		Water–acetone	61	69
4	**1c** (20)	 **7b**	—	86	93
5	**8** (30)		DMSO	74	65
6	**1c** (20)	 **7c**	—	96	94
7	**8** (30)		DMSO	94	69

[a] Reactions catalyzed by **1c** were carried out at 0 °C, while the other reactions were performed at room temperature.

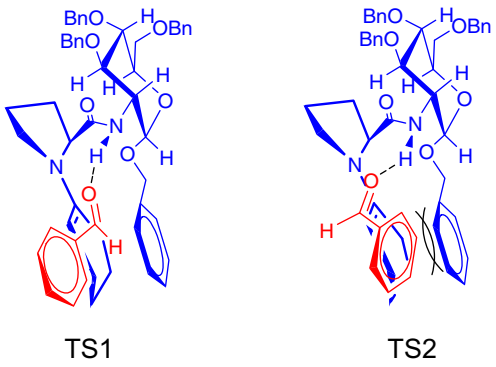


Figure 2. Plausible transition state.

To account for the stereochemical outcome of the current study, we propose that sugar-based prolinamide catalyst **1c** could catalyze the direct aldol reaction via the plausible transition state TS1 shown in Figure 2. The aldehyde could be activated by hydrogen bonding with NH at C-2 of glycon unit of the catalyst as shown in TS1 and TS2. The TS2 leading to the (1*S*,2*S*)-isomer is unfavoured since the approach of the aldehyde in the orientation shown is obstructed by the bulky α-benzyloxy group at the anomeric carbon of the sugar moiety on the catalyst framework. Consequently, the approach of the aldehyde in TS1 is facile since there are no such steric repulsions and the enantioselective C–C bond formation takes place on the *re*-face of the aldehyde leading to the production of the (1*R*,2*S*)-isomer.

3. Conclusion

In conclusion, we have demonstrated a mild and facile method for catalytic enantioselective aldol reaction between ketones and aromatic aldehydes using a sugar-derived prolinamide under solvent-free conditions. Currently we are exploring the applicability of the title organocatalyst in other catalytic transformations.

4. Experimental

4.1. Typical procedure for the enantioselective aldol reaction catalyzed by organocatalyst 1c

A solution of aldehyde (0.2 mmol), organocatalyst **1c** (0.04 mmol, 20 mol %) and cycloalkanone (3 mmol) was stirred for 5–48 h at 0 °C. The reaction was monitored by TLC at regular intervals. Upon completion of the reaction, the crude product was submitted for ^{1}H NMR (500 MHz) to determine the diastereomeric excess. The residue was subjected to column chromatography on silica gel to afford a pure product. The HPLC analysis of the aldol product was performed on a chiral stationary phase using hexane–isopropanol as eluting solvent.

Acknowledgements

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