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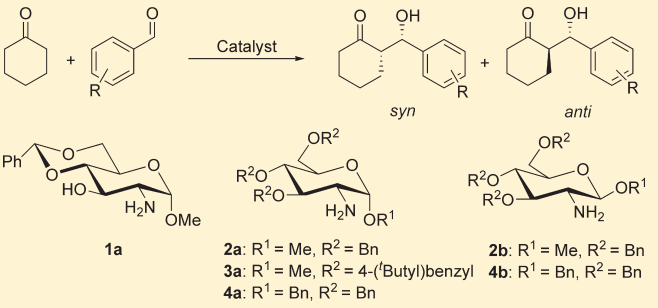
Glucosamine-Based Primary Amines as Organocatalysts for the Asymmetric Aldol Reaction

Jyoti Agarwal and Rama Krishna Peddinti*

Department of Chemistry, Indian Institute of Technology, Roorkee 247 667, Uttarakhand, India

Supporting Information

ABSTRACT: Glucosamine derivatives have been synthesized starting from commercially available *N*-acetyl-D-glucosamine/glucosamine hydrochloride and have been employed successfully as efficient organocatalysts for the direct asymmetric aldol reaction between cyclohexanone and aryl aldehydes having diversified substituents. Furthermore, the anomeric effect of various groups present at the anomeric position on the catalytic activity of these organocatalysts was also studied.



Carbohydrates have been widely used as chiral templates for introducing chirality in synthetic asymmetric processes owing to their rigid structure with high degree of functionalization and the presence of several contiguous stereogenic centers.[1] These molecules have been used in many reactions as chiral reagents or ligands and found to be superior to many other molecules.[2] Many metals such as Zn, Ti, Gd, Rh, etc. were complexed with these carbohydrate-based chiral ligands and their catalytic activity has been explored for numerous asymmetric transformations like Reformatsky reaction,[3] hydrogenation process,[4] Strecker reactions,[5] and alkylation of aldehydes.[6] In recent years, these sugar-based molecules have also been developed as organocatalysts in asymmetric synthesis. In these reports, mono- or disaccharides were employed as a chiral scaffold to obtain high optical yields. These sugar units were coupled either with a pyrrolidine ring through an amide bond[7] or to other chiral moieties through urea[8] /thiourea[9] linkage, where pyrrolidine −NH or another functional group such as the $-NH_2$ group was actively participating to catalyze the reaction through enamine/iminium catalysis and/or hydrogen bonding. However, to the best of our knowledge, these sugar-based molecules had never been used independently as bifunctional organocatalysts in asymmetric synthesis without attaching other chiral moieties such as proline and cyclohexyldiamine or metal ion except one report wherein commercially available glucosamine was employed for aldol reaction to obtain almost racemic products in most of the cases.[10]

In the literature, there are several reports where primary amines have been used to catalyze organic reactions.[11] Such glucosamine-based molecules have drawn our attention to study them as organocatalysts since these are leading source of contiguous stereogenic centers bearing a primary amino group and an hydroxy group that may be readily manipulated in configuration to allow rapid fine-tuning of their function. For our study, we chose the asymmetric direct intermolecular aldol reaction between aryl aldehydes and cyclohexanone.

Herein, we report the results of our studies on the effect of bulkiness as well as configuration (α- or β-) of the groups present at the anomeric position of the sugar catalyst on the enantioselectivity of the aldol product and the catalytic activity of fully protected sugar-based primary amine except at the C3 position on the asymmetric induction of the aldol reaction.

Initially, we synthesized catalyst **1a** according to the literature procedure[3a,12] as outlined in Scheme 1. *N*-Acetyl-D-glucosamine was converted to methyl *N*-acetyl-D-glucosamine by refluxing it in anhydrous MeOH with amberlyst IRN 120 H^+ resin,[12] which was further reacted with benzaldehyde dimethyl acetal followed by ethanolic KOH to obtain **1a**.[3a]

As a prelude to our objective, we evaluated glucosamine derivative **1a** as an organocatalyst for the aldol reaction between 3-nitrobenzaldehyde and cyclohexanone. As water is a green solvent, we used water as a medium for the aldol reaction. Thus the reaction was completed within 1 day with 91% yield but only 18% and 12% ee was obtained for *syn*- and *anti*-products, respectively (entry 5, Table 1). Then we screened other polar and nonpolar solvents to affect this transformation. The performance in terms of optical induction of the reactions carried out at room temperature was not encouraging. However, the reaction was found to be very fast when it was performed in neat conditions. Thus the reaction was completed within 3 h to yield 95% aldol adduct with 15% and 32% ee for the *syn*- and *anti*-products, respectively (entry 11, Table 1).

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Scheme 1. Synthesis of Methyl-2-amino-4,6-benzylidene-2-deoxy-α-D-glucopyranoside (1a)

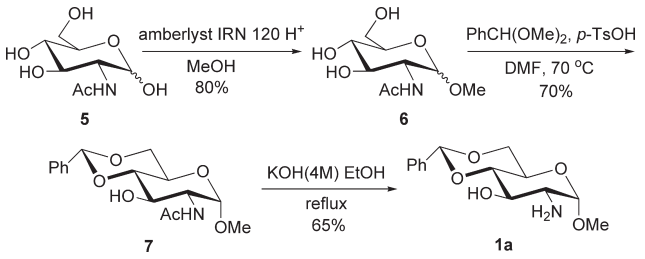
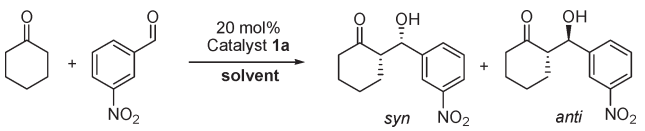


Table 1. Asymmetric Aldol Reaction between 3-Nitrobenzaldehyde and Cyclohexanone in the Presence of Organocatalyst 1a in Various Conditions[a]

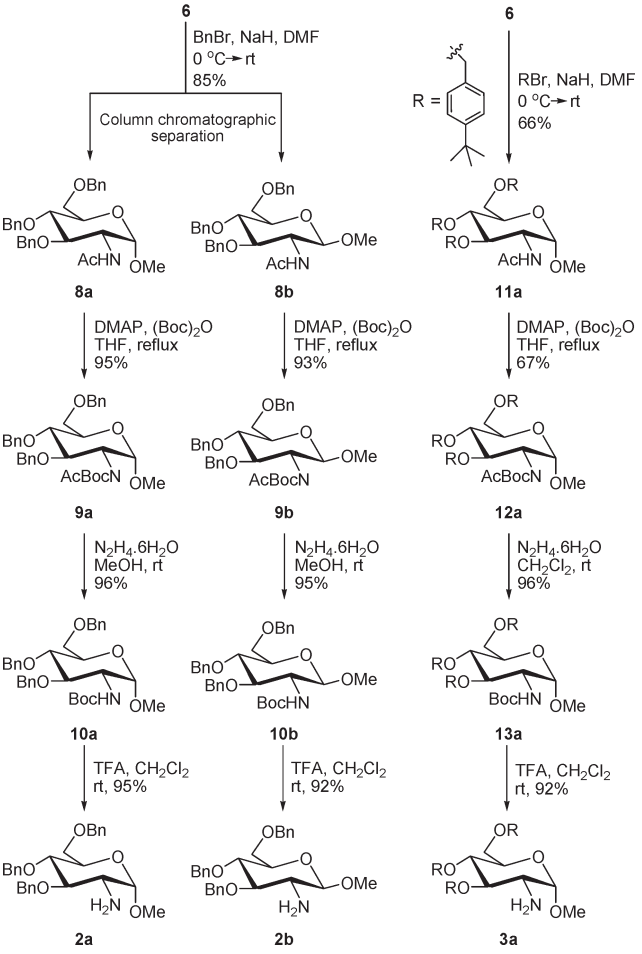


entry	solvent	temp (°C)	time	yield[b] (%)	dr[c] *syn*:*anti*	ee[d] *syn*	ee[d] *anti*
1	CH_3CN	rt	48	94	1.5:1	20	24
2	CH_2Cl_2	rt	48	96	1.5:1	0	4
3	MeOH	rt	72	92	0.8:1	0	2
4	$CHCl_3$	rt	48	90	1.2:1	14	17
5	H_2O	rt	24	91	0.7:1	18	12
6	DMSO	rt	96	90	1.3:1	10	20
7	DMSO:H_2O (4:1)	rt	24	88	2.4:1	2	20
8	DMSO:H_2O (2:1)	rt	96	90	1.5:1	8	16
9	CH_3CN	0	72	88	1.2:1	16	58
10	DMSO:H_2O	0	68	76	1.3:1	2	4
11	Neat	rt	3	95	1:1	15	32
12	Neat	0	8	98	1.9:1	30	60
13	CH_2Cl_2	0	96	91	1:3	15	35
14	H_2O	0	48	97	0.9:1	1	4

[a] Reactions were performed with cyclohexanone (0.4 mM) and 3-nitrobenzaldehyde (0.2 mM) in the presence of organocatalyst **1a** (0.04 mM) in 0.5 mL of solvent in entries 1−10, 13, and 14; cyclohexanone (0.3 mL) and 3-nitrobenzaldehyde (0.2 mM) were used in entries 11 and 12. [b] Yields are of pure and isolated products. [c] Determined by ^{1}H NMR of the crude sample. [d] Determined by HPLC analysis (Chiralcel OD-H).

Subsequently, we focused our attention on the effect of temperature on the outcome of the reaction anticipating better selectivity by lowering the reaction temperature. It was observed that with lowering the temperature, the enantioselectivity of the reaction was increased. For example, in neat condition, the ee value for the *anti*-product was 32% and 60% at room temperature and 0 °C, respectively. Encouraged by these results, we further reduced the reaction temperature and to our delight, at −20 °C we obtained *anti*-product in excellent optical yield of >99% when the reaction was performed in 15 equiv of cyclohexanone with 20 mol % catalyst loading. However, ee for the *syn*-product was

Scheme 2. Synthesis of Organocatalysts 2a, 2b, and 3b



not improved much. In general, as the reaction temperature was lowered to −20 °C, the rate of reaction was decreased without affecting the chemical yield much. However, further reduction in temperature to −40 °C resulted in lower enantioselectivity of the aldol adduct.

Next we examined the catalytic activity of fully *O*-protected sugar-based primary amines with both configurations, i.e., α- and β-anomers. For this purpose, we synthesized five glucosamine derivatives **2a**−**4b**. Chapleur reported[13] the synthesis of glucosamine derivative **2a** from α-anomer **8a**. As we needed both anomers **2a** and **2b**, we proceeded with the anomeric mixture **6**. Thus benzylation followed by column chromatographic separation provided α- and β-anomers **8a** and **8b** in 3:2 ratio. The reaction sequence described for the synthesis of **2a** was applied for the transformation of **8b** into **2b** (Scheme 2). When the protection of free hydroxyl groups of **6** with 4-*tert*-butylbenzyl bromide was carried out, we could isolate α-anomer **11a** only. The α-anomer **11a** was converted into glucosamine derivative **3a** following the three-step reaction sequence as shown in Scheme 2. Since the *N*-protected sugar derivative **12a** was less soluble in methanol, the deprotection of the *N*-acetyl group was performed in dichloromethane to furnish the corresponding α-anomer **13a** in excellent yield. The synthesis of β-anomer **4b**[14] was reported by Schmidt. However, we have synthesized both the monosaccharides **4a** and **4b** in 2:3 ratio from a common starting material

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Scheme 3. Synthesis of Organocatalysts 4a and 4b

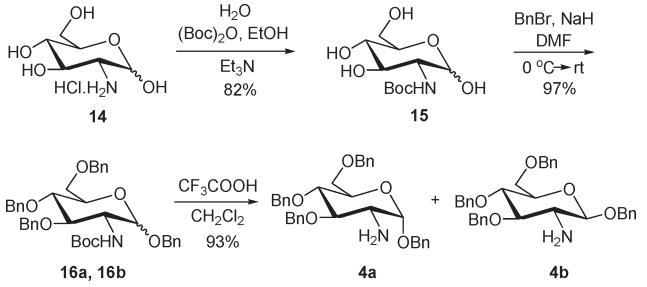
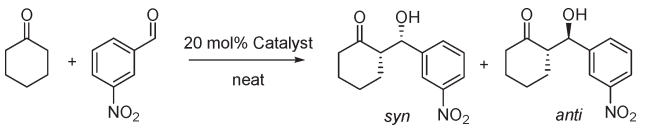


Table 2. Screening of Various Catalysts at Different Temperature for Aldol Reaction between Cyclohexanone and 3-Nitrobenzaldehyde[a]

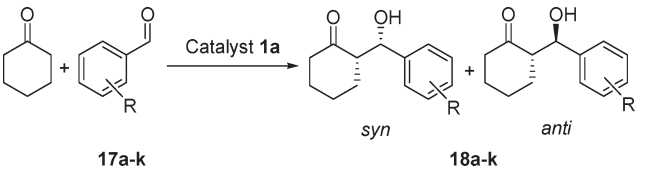


entry	catalyst	temp (°C)	time (h)	yield[b] (%)	dr[c] *syn*:*anti*	ee (%)[d] *syn*	ee (%)[d] *anti*
1	**1a**	0	8	98	1.9:1	30	60
2	**1a**	−20	16	96	0.8:1	33	99
3	**1a**	−40	24	98	1.4:1	16	94
4	**2a**	0	30	85	1.5:1	35	40
5	**2a**	−20	48	80	1.2:1	60	68
6	**2b**	0	72	39	4:1	50	38
7	**3a**	0	30	83	1.5:1	38	40
8	**3a**	−20	48	78	1.2:1	59	65
9	**4a**	0	48	80	2.1:1	30	35
10	**4a**	−20	72	70	2.3:1	36	42
11	**4b**	0	72	51	2.3:1	30	30

[a] Reactions were performed with 3-nitrobenzaldehyde (0.2 mM) and cyclohexanone (0.3 mL) in the presence of organocatalyst (0.04 mM). [b] Yields are of pure and isolated products. [c] Determined by ^{1}H NMR (500 MHz) of the crude sample. [d] Determined by HPLC analysis (Chiralcel OD-H).

D-glucosamine hydrochloride following a new pathway described in Scheme 3. The catalytic activity of these primary amine organocatalysts was tested at 0 and −20 °C for the reaction between cyclohexanone and 3-nitrobenzaldehyde (Table 2). When the catalyst **2a** was employed in the reaction at 0 °C, 85% yield of aldol product **18b** was obtained in 30 h with 35% and 40% ee for *syn*- and *anti*-isomers, respectively. However, in the presence of **2b**, the reaction was not complete even after 72 h at 0 °C and yielded 39% of the product **18b** with 50% and 38% ee of *syn*- and *anti*-isomers, respectively (Table 2, entries 4 and 6). Further, to improve the enantioselectivity of the reaction, the reaction was performed at −20 °C in the presence of organocatalyst **2a** to afford *syn*- and *anti*-isomers **18b** in a combined yield of 80% with 60% and 68% ee, respectively. The catalyst tri-*O*-(4-*tert*-butylbenzyl) sugar derivative **3a** did not influence the enantioselectivity of the reaction much. At this juncture, the

Table 3. Asymmetric Aldol Reaction between Cyclohexanone and Various Aryl Aldehydes Catalyzed by Organocatalyst 1a



entry	R	temp (°C)	time (h)	product	yield[a] (%)	dr[b] *syn*:*anti*	ee (%)[c] *syn*	ee (%)[c] *anti*
1	2-NO_2	−20	22	**18a**	94	2:1	84	81
2	2-NO_2	−40	24	**18a**	90	1.2:1	71	78
3	3-NO_2	−20	12	**18b**	98	0.8:1	33	>99
4	3-NO_2	−40	23	**18b**	95	1.4:1	16	94
5	4-NO_2	−20	12	**18c**	97	2:1	26	66
6	4-Br	−20	48	**18d**	90	1.3:1	39	92
7	2-Cl	−20	72	**18e**	82	1.6:1	90	96
8	4-Cl	−20	48	**18f**	85	1.1:1	62	92
9	4-CN	−20	16	**18g**	95	1:1	11	47
10	4-F	−20	48	**18h**	93	1:1	37	93
11	2-OMe	−20	72	**18i**	80	0.9:1	20	98
12	3-CF_3	−20	24	**18j**	85	1.4:1	27	62
13	4-CF_3	−20	16	**18k**	97	1:1	14	70

[a] Pure and column chromatographically isolated yields. [b] Determined by ^{1}H NMR of the crude sample. [c] ee values of *syn*- and *anti*-products determined by HPLC analysis.

catalytic activity of catalysts **4a** and **4b** was tested for the reaction. The replacement of the anomeric methyl group with the benzyl group lowered the enantioselectivity of the reaction (Table 2, entries 9, 10, and 11). It was observed that the catalytic activity of α-anomers was better than that of β-anomers (Table 2). Thus, the screening of the catalysts in various solvents and neat condition and at different temperatures identified optimal conditions and **1a** as the optimal catalyst to carry out further asymmetric aldol reaction.

To explore the versatility of the organocatalyst **1a**, a variety of aromatic aldehydes bearing diversified substituents were employed as aldol acceptors in the presence of 20 mol % catalyst **1a** at −20 °C. The reaction worked well with aromatic aldehydes bearing both electron-releasing as well as electron-withdrawing groups to afford aldol adducts **18a**−**k** in high to excellent chemical yields with high to excellent enantioselectivities for *anti*-products and low to good enantioselectivities for *syn*-products. Furthermore, the rate of the reaction was found to be dependent not only upon the elecronic nature of the substituents on the aromatic nucleus but also on their position on the arene moiety. For example, aldol reaction between cyclohexanone and 2-nitobezaldehyde afforded aldol product **18a** in 22 h with 94% chemical yield with 84% and 81% optical yield for *syn*- and *anti*-adducts, respectively, at −20 °C (Table 3, entry 1). The 4-nitrobenzaldehyde gave rise to aldol product **18c** in 12 h with near-quantitative yield and moderate enantioselectivity (Table 3, entry 5). The better asymmetric induction in the reaction of the 2-nitro derivative can be explained on the basis of steric

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hindrance resulting from ortho-substitution for enhanced differentiation of enantiomers. The halo-substituted benzaldehydes also provided the corresponding aldol adducts **18d**,**e**,**f**,**h** in very high to excellent chemical yields. The reaction of 2-chlorobenzaldehyde (**17e**) was slower than that of 4-chlorobenzaldehyde (**17f**); however, in both cases good to excellent enantioselectivities were obtained for both *syn*- and *anti*-isomers. The 4-bromo- and 4-fluorobenzaldehydes also afforded corresponding aldol adducts **18d**, **18h** with high enantioselectivity of *anti*-products, but moderate enantioselectivity was obtained for *syn*-products. In the case of electron-donating substituent, i.e. a 4-methoxy group, the reaction was completed in 72 h to provide 80% of aldol product **18i** and *syn*- and *anti*-products were obtained with 20% and 98% enantioselectivity, respectively.

The reaction between acetone and 4-nitrobenzaldehyde was also carried out in the presence of catalyst **1a**. However, the asymmetric induction was not impressive. The reaction was performed at 0 and −20 °C to produce the aldol product in 35% ee (18 h, 93%) and 66% ee (48 h, 85%), respectively.

In conclusion, for the first time, a bifunctional sugar-based primary amine was employed independently as an efficient and potential organocatalyst for the asymmetric transformation. We observed that the sugar catalyst **1a** bearing a free hydroxyl group vicinal to primary amine functionality was the optimal catalyst for our study and it provides the best results possibly through the hydrogen bonding between the proton on the hydroxyl moiety and the carbonyl group of the aldehyde. This situation could be analogous to the functional group array of proline, especially in light of the reduced pK_a of carbohydrate hydroxyls relative to simple secondary alcohols. We have also studied the anomeric effect of sugar-based molecules **2a** and **2b**, **4a**, and **4b** on the rate of reaction as well as on the optical induction of the aldol adduct and found that α-anomers catalyze the reaction faster than the β-anomers. As these derivatives have been shown to be promising organocatalysts for direct asymmetric aldol reactions it provides us an opportunity to explore their catalytic activity for other asymmetric transformations in due course.

EXPERIMENTAL SECTION

General Procedure for the Aldol Reaction. To the solution of organocatalyst **1a** (0.04 mM, 20 mol %) in cyclohexanone (0.3 mL) was added aryl aldehyde (0.2 mM) and the resulting reaction mixture was stirred for a certain time (as mentioned in Table 3) at −20 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, crude product was submitted to ^{1}H NMR (500 MHz) spectroscopy to obtain a diastereomeric ratio of *syn*- and *anti*-products. Then the reaction mixture was subjected to silica gel chromatography to afford the corresponding products **18a**−**k** in pure form. The HPLC analysis of the aldol products was performed on a chiral stationary phase with hexane−isopropanol as the eluting solvent.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data of new compounds, HPLC data table and chromatograms for aldol products, and copies of ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra of all compounds; and 500 MHz ^{1}H−^{1}H COSY and 125 MHz HETCOR spectra of **4a** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: rkpedfcy@iitr.ernet.in.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published to the Web on March 21, 2011, with errors in the abstract graphic and scheme 1. These errors were fixed when the paper was published to the Web on March 29, 2011.