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Highly Enantioselective Organocatalytic *syn*- and *anti*-Aldol Reactions in Aqueous Medium

Monika Raj,[a] Gopal S. Parashari,[a] and Vinod K. Singh[a,*]

[a] Deparment of Chemistry, Indian Institute of Technology, Kanpur – 208016, India
Fax: (+91)-512-259-7436; e-mail: vinodks@iitk.ac.in

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Abstract: We have synthesized chiral diamines that efficiently catalyze the *syn*- and *anti*-aldol reactions in aqueous medium with high diastereo- and enantioselectivities. The product, thus obtained, was further reduced selectively to give *syn*-configured 1,2,3-triol, an important subunit present in various monosaccharides and natural products such as (+)-boronolide.

Keywords: aqueous medium; mimicking enzymes; primary-tertiary diamines; quaternary stereocenters; *syn*- and *anti*-aldol reaction

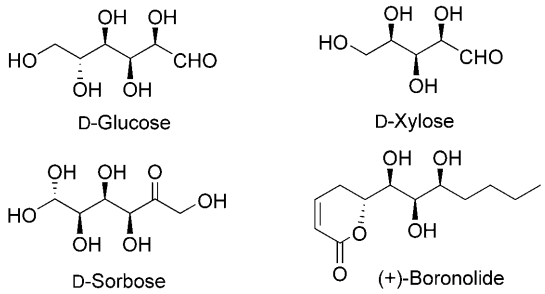


Figure 1. *syn*-1,2,3-Triol is a very common subunit.

For the last few years, researchers have been interested in synthesizing organocatalysts, mimicking enzymatic activities.[1] The continued interest of our group[2] to understand carbohydrate chemistry has motivated us to design such organocatalysts that imitate the enzymes involved in monosaccharide synthesis. The most abundant monosaccharide in nature is the six carbon sugar, D-glucose.[3] The chain form of glucose is a polyhydric aldehyde, meaning that it has multiple hydroxy groups and an aldehyde group. The stereochemistry of these hydroxy groups is very important as many saccharide structures differ only in the orientation of the hydroxy groups which makes a big difference in the biochemical, organoleptic (e.g., taste), and physical properties such as melting point and specific rotation.[3] In D-glucose, three hydroxy groups at positions 2, 3 and 4 are in a *syn* configuration (Figure 1). In gluconeogenesis, enzymes such as fructose biphosphate aldolases, fructose 1,6-bisphosphatase and glucose 6-phosphatase are involved in synthesizing the *syn*-configured 1,2,3-triol moiety,[3] which is an important subunit present in other monosaccharides such as D-sorbose, D-xylose and natural products such as (+)-boronolide (Figure 1). Thus, expansion of the scope and efficency of the synthesis of this kind of moiety is of great importance.

The synthesis of such polyhydroxy units can be carried out by an organocatalyzed enantioselective aldol reaction with unprotected hydroxyacetone which gives both *anti*- and *syn*-configured 1,2-diols. The *anti*-configured 1,2-diol is readily accessible by using proline- or pyrollidine-catalyzed reactions.[4] An organocatalytic approach to the *syn*-configured 1,2-diol with unprotected hydroxyacetone was recently reported by Barbas et al.[5] The main limitation associated with this *syn*-aldol reaction[5] is the requirement of a high catalyst loading. Although some of these catalysts gave good results in organic medium,[5,6] they failed to give promising results in aqueous medium with unprotected hydroxyacetone. Therefore, there is a need for such organocatalysts that work well in aqueous medium, thus mimicking the enzymes involved in gluconeogenesis. In our earlier studies, we have successfully developed organocatalysts for a variety of reactions (including aldol[7] and Michael[8]) that work efficiently in both organic and aqueous medium.

Given the success of primary-tertiary diamine-based catalysts for aldol reactions of linear aliphatic ketones pioneered by Cheng et al.,[9a] we designed another series of primary-tertiary diamines, containing the aromatic groups for the asymmetric *syn*-aldol reaction of unprotected hydroxyacetone in the presence

of water. The idea behind this design is that these aromatic groups will form a hydrophobic cavity with the reactants in aqueous medium.[9b] Thus, the reaction will successfully take place in this cavity, resulting in high enantioselectivity and diastereoselectivity in aqueous medium.

In this paper, we report our strategy for the successful diastereo- and enantioselective organocatalytic reaction with unprotected hydroxyacetone in water to obtain the *syn*-configured 1,2-diol. The *syn*-diol thus obtained is further used to synthesize the *syn*-configured 1,2,3-triol by a selective reduction process.

From the previous studies[7,8] we anticipated that this hydroxyacetone may give the *syn*-aldol product through a *Z*-enamine intermediate[10] because of its stablization by hydrogen bonding with the hydrogen of the primary amino group, which is not possible in the reactions catalyzed by secondary amine-based catalysts. On the other hand, for cyclic ketones which are capable of forming only the *E*-enamine,[6] the *anti*-aldol product would be expected by the same type of catalysts (Figure 2). To verify the proposed

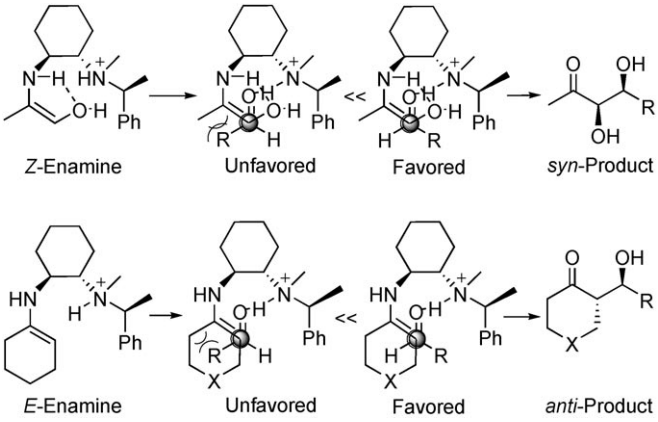
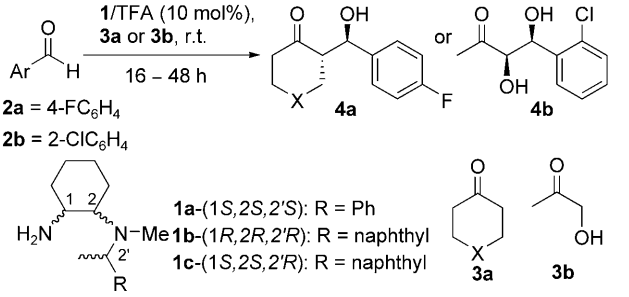


Figure 2. Plausible transition states for *syn*- and *anti*-aldol adducts.

hypothesis, a series of chiral primary-tertiary amines was synthesized from cyclohexene oxide and chiral amines (see Supporting Information for details) and were then examined on both hydroxyacetone and cyclohexanone in an aqueous medium at room temperature (Table 1). It was found that as the amount of donor ketone was reduced from four to two equivalents relative to the acceptor aldehyde, the enantioselectivity of the reaction increased to >99% (entries 1 and 2).

The observations collated in Table 1 revealed that the presence of a strong Brønsted acid such as TFA is essential for getting high diastereo- and enantioselectivity, as the reaction without any acid resulted in low yield and selectivity (entry 3). From the Table 1, it becomes clear that the chirality of methylbenzylamine

Table 1. Selected screening results.

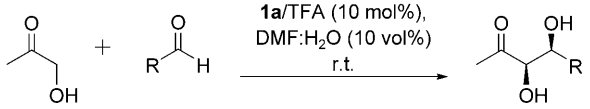


Entry	Cat.	Solvent	Yield [%][a]	*anti:syn*[b]	*ee* [%][c]
1[d]	**1a**	H_2O	**4a**/77	92:8	98
2	**1a**	H_2O	**4a**/74	97:3	>99
3[e]	**1a**	H_2O	**4a**/52	83:17	73
4[f]	**1b**	H_2O	**4a**/74	89:11	97
5	**1c**	H_2O	**4a**/79	91:9	98
6	**1a**	DMF	**4b**/80	5:95	96
7	**1a**	DMF:H_2O (3%)	**4b**/82	3:97	98
8	**1a**	DMF:H_2O (6%)	**4b**/80	3:97	99
9	**1a**	DMF:H_2O (10%)	**4b**/83	2:98	>99
10	**1a**	DMF:H_2O (25%)	**4b**/79	2:98	97
11	**1a**	DMF:H_2O (50%)	**4b**/75	3:97	97
12	**1a**	DMF:H_2O (75%)	**4b**/75	3:97	96
13	**1a**	H_2O	**4b**/71	7:93	86
14	**1a**	brine	**4b**/73	8:92	86

[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC using chiral columns.
[d] Four equivalents of ketone was used.
[e] Without TFA.
[f] Opposite enantiomer.

does not play any significant role on the selectivity of the aldol reactions (entries 2 and 5). Furthermore, it was observed that organic compound **1a** is slightly more efficient in inducing asymmetric induction in the aldol reaction of 4-fluorobenzaldehyde and cyclohexanone (entry 2). So, we chose catalyst **1a** for further screening of the reaction under the optimal reaction conditions for hydroxyacetone (Table 1, entry 9) with various acceptor aldehydes (Table 2). It was found that reactive aldehydes gave good yields and excellent diastereo- and enantioselectivities (Table 2, entries 1–7). Although the reactions with less reactive aldehydes such as cyclohexane carboxyaldehyde proceeded slowly, good yields and stereoselectivity were observed (Table 2, entry 8). In order to show the practicality of the method, the reaction was tested on a large scale. Hydroxyacetone (4.86 mL, 71.1 mmol) was allowed to react with 2-chlorobenzaldehyde (4 mL, 35.6 mmol) by using catalyst **1a** (825 mg, 10 mol%) and TFA (0.265 mL, 10 mol%) in DMF:water (10 vol%) (36 mL) at room temperature. The reaction was completed in 24 h and the *syn*-aldol product was obtained in 87% yield and >99% *ee*.

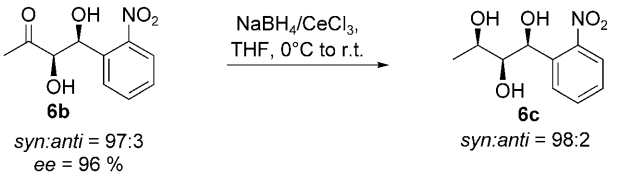
Table 2. *syn*-Aldol reaction of unprotected hydroxyacetone in the presence of water.



Entry	R	Yield [%][a]	*syn:anti*[b]	*ee* [%][c]
1	Ph	**5b**/83	96:4	96
2	2-$NO_2C_6H_4$	**6b**/85	97:3	98
3	3-BrC_6H_4	**7b**/79	97:3	>99
4	4-$CF_3C_6H_4$	**8b**/86	95:5	94
5	3-Cl-4-FC_6H_3	**9b**/89	96:4	94
6	4-CNC_6H_4	**10b**/85	98:2	93
7	4-$NO_2C_6H_4$	**11b**/87	95:5	91
8	cyclohexyl	**12b**/87	98:2	96

[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC using chiral columns.

The *syn*-aldol product obtained from hydroxyacetone and 2-nitrobenzaldehyde was then subjected to selective reduction. It was found that sodium borohydride/cerium chloride, reduced the carbonyl group of the *syn*-aldol product selectively to give the *syn*-configured 1,2,3-triol (in a diastereomeric ratio of 98:2, Scheme 1, see Supporting Information for details), an

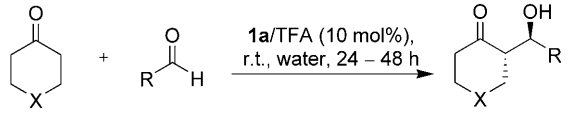


Scheme 1. Selective reduction to the *syn*-configured 1,2,3-triol.

important subunit present in various monosaccharides and natural products as shown in Figure 1. Under optimized conditions for the *anti*-aldol reaction (Table 1, entry 2), catalyst **1a**/TFA was explored on different sets of aldehydes and cyclic ketones to determine the general synthetic utility (Table 3). The results demonstrated the flexibility of the catalyst with respect to both aldehydes and cyclic ketones. Importantly, heteroaromatic aldehyde such as thiophene-2-carboxyaldehyde also acted as a worthy substrate. In all the cases the reaction afforded *anti*-aldol products with high diastereo-and enantioselectivities (Table 3.).

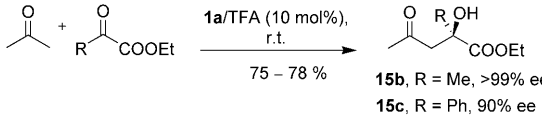
Next, we focused our attention on the intermolecular cross-aldol reaction of two ketones.[11] We attempted a rare example of the aldol reaction of two ketones, where ketones act as both donor and acceptor. The reaction of acetone and the keto ester was performed without any preactivation of acetone as a silyl

Table 3. *anti*-Aldol reaction of cyclic ketones in water.



Entry	X	R	Yield [%][a]	*anti: syn*[b]	*ee* [%][c]
1	$-CH_2-$	Ph	**5a**/85	97:3	97
2	$-CH_2-$	4-$OMeC_6H_4$	**6a**/78	99:1	92
3	$-CH_2-$	4-$CF_3C_6H_4$	**7a**/90	92:8	97
4	$-CH_2-$	4-CNC_6H_4	**8a**/89	95:5	97
5	$-CH_2-$	4-MeC_6H_4	**9a**/76	98:2	92
6	$-CH_2-$	2-naphthyl	**10a**/83	96:4	97
7	$-O-$	4-FC_6H_4	**11a**/81	86:14	90
8	$-O-$	4-CNC_6H_4	**12a**/85	95:5	91
9	$-O-$	2-thiophenyl	**13a**/76	98:2	96
10	$-S-$	4-FC_6H_4	**14a**/80	99:1	94
11	$-S-$	2-thiophenyl	**15a**/79	96:4	99

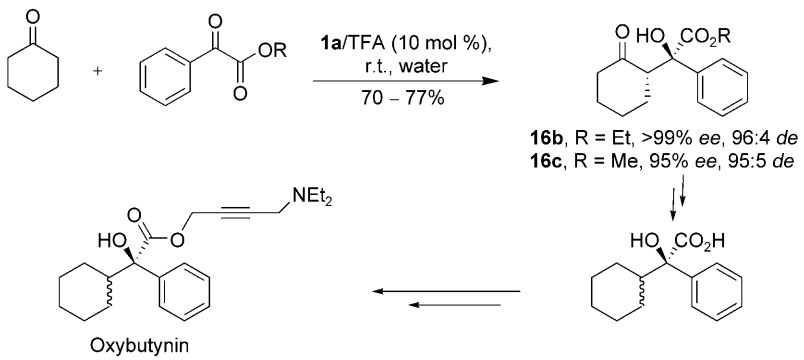
[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC using chiral columns.



Scheme 2. Rare example of an aldol reaction of two ketones.

enol ether.[11a,b] We found that the reaction of acetone and ethyl pyruvate generated the crucial quaternary carbon with a high enantioselectivity of >99% at room temperature under neat conditions. Similarly, reaction of acetone with ethyl phenyl glyoxylate also gave the product with high yield and enantioselectivity (78% yield, 90% *ee*) (Scheme 2).

Encouraged by these results, the reaction of cyclohexanone and phenyl glyoxylate was carried out to generate the crucial chiral tetrasubstituted carbon center in aqueous medium (Scheme 3). In this reaction cyclohexanone acts as a donor and ethyl phenyl glyoxylate acts as an acceptor. Gratifyingly, we found that the reaction with a catalytic amount of **1a**/TFA (10 mol%) in water at room temperature gave the desired aldol product with good yield and excellent diastereoselectivity and enantioselectivity (96:4 *de*, >99% *ee*, Scheme 3). Similarly, the reaction of methyl phenyl glyoxylate and cyclohexanone also gave the product with excellent diastereoselectivity and enantioselectivity (95:5 *de*, 95% *ee*, Scheme 3). Significantly, the aldol adducts thus obtained can further be converted into 2-cyclohexyl-2-phenylglycolic acid by a known reaction sequence.[12] This 2-cyclohexyl-2-phenylglycolic acid serves as a key intermedi-



Scheme 3. Application in the synthesis of oxybutynin.

ate for the synthesis of oxybutynin, which is a widely prescribed muscarinic receptor antagonist for the treatment of urinary frequency, urgency and urge incontinence (Scheme 3).

In summary, we have developed organocatalysts that efficiently catalyze the *syn*-aldol reactions of unprotected hydroxyacetone with high diastereo- and enantioselectivities in aqueous medium. The *syn*-product thus obtained, was reduced selectively to obtain the *syn*-configured 1,2,3-triol, a subunit present in various monosaccharides and natural products. These catalysts also efficiently and selectively catalyze *anti*-aldol reactions of cyclic ketones in water. Furthermore, these catalysts carried out the unusual aldol reaction of two ketones to generate the crucial chiral quaternary carbon center and oxybutynin that acts as a muscarinic receptor antagonist.

Since these primary-tertiary diamines gave good results with a variety of donors and acceptors they are in contrast with the type I aldolase enzyme, i.e., fructose 1,6-biphosphate aldolase that is limited to the use of dihydroxyacetone phosphate as the aldol donor substrate. Thus, these catalysts not only mimic but function better than type I aldolases.

Experimental Section

Representative Procedure for Direct Aldol Reaction of Unprotected Hydroxyacetone with Catalyst in Water

To a mixture of organocatalyst **1** (10 mol%) and ketone (2 mmol) in an round-bottomed flask, DMF:water (10 vol%) (1.0 mL) was added at room temperature followed by addition of TFA (10 mol%). To this an aldehyde (1 mmol) was added after 30 min and the reaction mixture was stirred and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was partitioned between a saturated solution of ammonium chloride and dichloromethane. The organic layer was separated and dried over anhydrous Na_2SO_4. It was purified over silica gel by column chromatography to obtain the pure product. The enantiomeric excess (*ee*) of aldol product was determined by chiral HPLC analysis. Relative and absolute configurations of the products were determined by comparison with known ^{1}H NMR, chiral HPLC analytical, and optical rotation values.

Acknowledgements

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