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Organocatalysis with Glycosyl Amino acids: Direct Asymmetric Aldol Reaction of Acetone with Aldehydes[+]

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Abstract: Direct asymmetric aldol reaction of acetone with aromatic aldehydes using hitherto unprecedented glycosyl acyclic amino acid as a new organocatalyst with high enantioselectivity and good yields is reported.

Key words: Aldol reactions, Aldehydes, Catalysis, Organometallic Asymmetric catalysis

The concept of molecular recognition, supramolecular chemistry and the fact that several enzymes do not carry a metal binding site led to the emergence organocatalysts, the smallest enzyme.[1] Organocatalysts have long been neglected inspite of the fact that many stereoselective reactions are catalysed by them efficeintly.[2] Undoubtedly, the organometallic catalysts despite some of perhaps the less important limitations are reasonably well developed, but there are many problems with organometallic catalysts in terms of the production process in chemical and pharmaceutical industry and metal toxicity in chemotherapeutic agents.[3] The aldol reaction, widely regarded as one of the most powerful C-C bond forming reactions has extensively been used for stereoselective synthesis of β-hydroxy carbonyl and 1,3-diol units found in complex polyols architectures of natural products[4] by Evans, [5] Heathcock,[6] Masamune, [7] Mukaiyama, [8] List and Barbas [9] groups.

A number of reports exist in the literature where the reaction between an aldehyde and ketone results in a β-hydroxy ketone involving different techniques. The methodologies developed so far are based on the mechanism involved during aldolase catalysis, where the basic (-NH_2) group from the enzyme abstracts a proton from the ketone and Zn^{++} required during enzymatic reactions complexes with the carbonyl group of the aldehyde to give an enolate for attack by the α-carbanion of the ketone. In general, the asymmetric aldol reactions can be categorized into the following five types, (i) chiral auxiliary assisted aldol reaction based on the use of stoichiometric quantities of the chiral appendages; (ii) chiral Lewis acid and Lewis base catalysed (iii) heterobimetallic bifunctional Lewis acid/Bronsted base catalysed aldol reeactions (iv) Enzyme or antibody catalysed reaction and (v) organocatalysis with L-proline or its structural analogs. Out of these methods the above three methods (i-iii) have successfully been used with the unmodified carbonyl compounds while the two methods (iv-v) require some sort of pre-activation of the carbonyl group of the ketones used for successful operations. Pioneering work on asymmetric aldol reaction with antibodies[10] and class I aldolases[11] have unambiguously established that the reaction is facilitated by amine based enamine formation.

Organocatalysis[1] with small molecules in direct aldol reactions has been known very recently, however, the biggest breakthrough came in this area when L-proline was reported as an effective catalyst for direct asymmetric aldol reaction.[9f] Since then, several dipeptides, amino alcohols and amino acids bearing a cyclic. pyrrolidine moiety were used as organocatalysts successfully for asymmetric aldol reactions with different substrates. Gong and Wu's[12] group in China has shown successful asymmetric Aldol reaction of 4-nitrobenzaldehyde and acetone catalysed by small organic molecules derived from L-prolinamide bearing chiral amino alcohol residues.

In all of the above studies it has been speculated that a cyclic secondary amine (pyrrolidine) and an alcoholic or carboxylic group at C-2 or in a chain attached to C-2 capable of donating a proton are essential for success of the reaction. However, we found that a cyclic secondary amine.

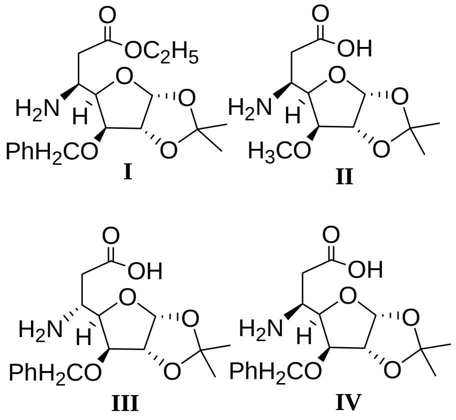
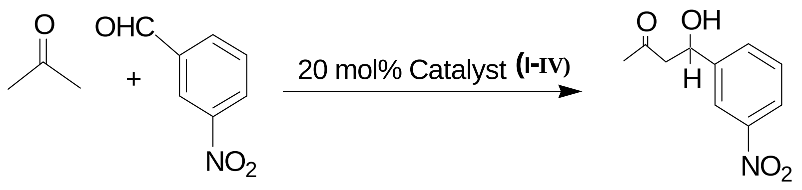


Figure 1 Glycosyl amino acid derivatives used as organocatalyst

is not the critical requirement for the above reaction as β-glycosyl β-amino acids[13,14] bearing 3-*O*-benzyl/mehyl α-D-xylopentofuranosyl moieties, recently synthesized by us as antitubercular agent exhibit increased enantioselectivity in aldol reaction of different aromatic aldehydes and acetone

Carbohydr. Res. 341, 2737 (2006)



Scheme 1. Aldol reaction of3-nitrobenzaldehydes with acetone in presence of 20 mol % of catalyst **IV**

We carried out the reaction of 3-nitro benzaldehyde with acetone in presence of in presence 20 mol % of glycosyl amino acid and their respective ester derivatives **I**-**IV** (Figure 1*)* separately as organocatalysts under different experimental conditions. Among all the above amino acid derivatives, glycosyl amino acid **IV** proved to be of high catalytic efficiency as the yield was 65 % with 90 % ee. The reaction of 3-nitro benzaldehyde with acetone in presence of organocatalyst **III** with opposite configuration at the amine carbon was sluggish as compared to that of compound **IV** at ambient temperature and the enantioselectivity was 68 % only, as evident from HPLC of the product isolated by column chromatography. However, the reaction of 3-nitro benzaldehyde with acetone using compound **I** as an organocatalyst did not proceed at all under the above reaction condition. The glycosyl amino acid **II** having 3-O-methyl substituent in the furanose ring, when used as organocatalyst resulted in 55 % yield with only 18 % enantioselectivity.

This observation is in accordance with the fact that hydrophobic active site plays a key role in functioning of aldolase antibodies.[6d] The results are summarized in Table-1

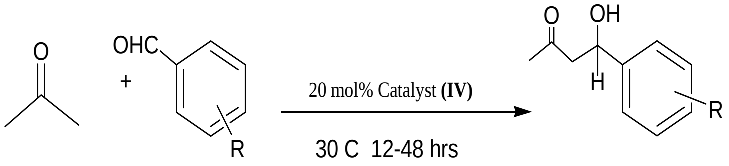
Table 1. Reaction of 3-nitro benzaldehyde with acetone under influence of different Amino acids

Entry	**Catalyst**	**Temp**	**% ee**	**Yield % (mol % of the catalyst)**
1	**I**	0-60 ^{0}C	-	No reaction
2	**II**	30 ^{0}C	18	59
3	**III**	30 ^{0}C	_	No reaction
		60 ^{0}C	68	55
4	**IV**	30 ^{0}C	-	10 (10)
		30 ^{0}C	90	69 (20)
		30 ^{0}C	90	65 (50)

The above reaction of 3-nitrobenzaldehyde with acetone in presence of glycosyl aminoacid **IV** was carried out under different experimental variants such as solvent, temperature and quantity of the catalyst. In DMF, acetonitirle, THF and water the above reaction did not proceed at ambient temperature even after 9 hr and we did not pursue it further. However, in DMSO the formation of aldol product started only after 9 hr and reaction was complete only after 30 hr, but the isolation of the aldol product was difficult in this case as compared to neat acetone. The above reaction was also carried out under the influence of 10 and 50 mol % of the organocatalys **IV**. While the former led to low yield of the product the latter did not lead to any improvement in the yield of the desired product. The above reaction did not proceed 6 at 0 ^{o}C it even after hrs.

To see the generality of the above glycosyl amino acid **IV** as an organocatalyst in direct asymmetric aldol reaction a variety of aromatic aldehydes with different substituents were reacted with neat acetone under above mentioned optimal reaction conditions (Scheme 2). The results are depicted in table 2. All the reactions were catalysed by 20 mol % of the glycosyl amino acid at ambient temperature. Both the highest yield (67 %) and maximum enantioselection (99%) was observed with 2-nitro benzaldehyde.

In few of the reactions of acetone and aldehydes dehydrated products were also obtained along with the aldol products. The ratio of dehydrated products were increased wih increase in temperature and the enantioselectivities in the aldol products were also sacrificed.



Scheme 2. Aldol Products of different aldehydes with acetone in presence of 20 mol % of catalyst **IV**

Table 2. Aldol Products of different aldehydes with acetone in presence of 20 mol % of catalyst **IV**

[a] Yield represents the combined yield of enantiomers

[b] Determined by HPLC [c] Conducted at 23 ^{0} C

.[d] ee in DMSO [e] ee in Neat acetone

Reaction Mechanism As proposed by Barbas III et al. we presume that the reaction proceeds (Figure 2) via formation of an enamine (**A**) between glycosyl amino acid and acetone. The formed enamine then attacks the carbonyl group of the aldehyde acceptor with high enantiofacial selectivity, because of a highly organized bicyclic hydrogen bonded transition state (**B**) that resembles the metal free Zimmerman-Traxler type transition state. Additon of water followed by elimination of the catalyst results in aldol products (**C**). The above proposed mechanism is in accordance with our observation that both amine and acidic proton are required for catalysis as with glycosyl amino esters I the reaction did not proceed. different glycosyl amino acids

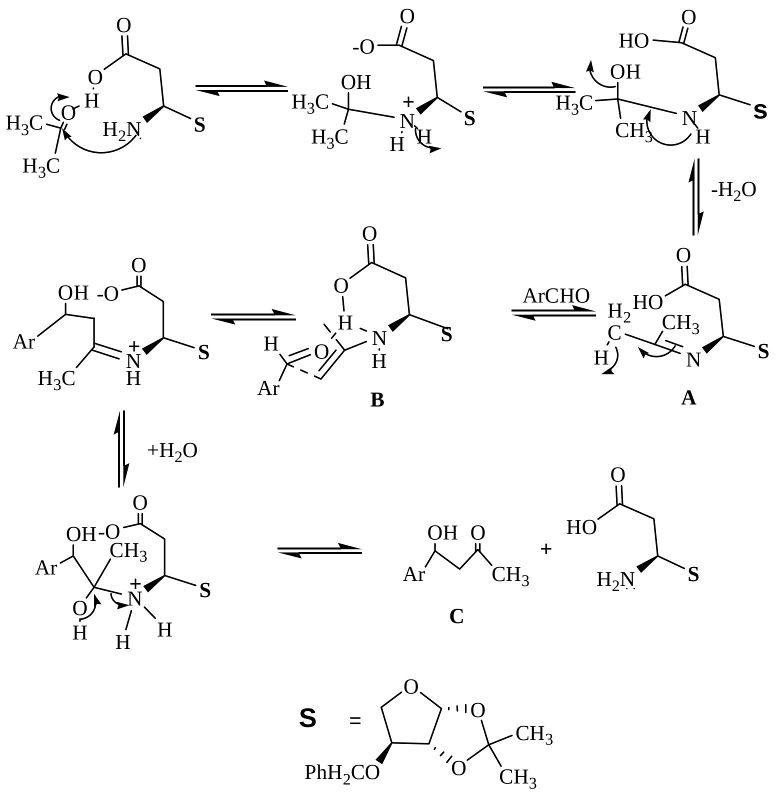


Figure2 Reaction Mechanism for aldol reaction

General procedure for Aldol reaction: To a stirring solution of anhydrous acetone (3 mL) and the required aldehyde (1 mmol), glycosyl amino acid (20mol %) was added. The reaction mixture was stirred at ambient temperature for 8-36 h. The solvent evaporated and the residue was purified through flash column chromatography on a silica gel hexane: ethyl acetate (1: 3) as eluent to give the pure adducts**.**

4-Hydroxy-4-(3'-Nitrophenyl)-butan-2-one (**1a**): Yield: 65%; $[\alpha]^{27}_{D}$ +22^{0} (*c* = 0.5, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.23 (s, 3H), 2.88 (m, 2H), 3.60 (d, *J*= 3.1Hz, exchangeable 1H), 5.26 (m, 1H), 7.53 (t, *J*=9.2 Hz 1H), 7.71 (d *J*=7.7Hz , 1H), 8.14 (d, *J*= 8.1 1H), 8.24 (s, 1H), ^{13}C NMR (50 MHz, CDCl$_3$): δ 31.0, 51.9, 69.1, 121.0, 122.8, 129.8, 132.2, 145.5, 148.7 208.9; FABMS *m/z* = 210 (M+H)$^{+}$; IR (Neat) 3423.2, 1710.5 1218.2. cm^{-1}. Enantiomeric excess 90 %, determined by HPLC (Chiradex column, CH$_3$CN/Water = 90/10), UV 254, flow rate 0.7mL/min. Minor; t_R 3.31 and major; t_R 3.63.

4-Hydroxy-4-(2'-Nitrophenyl)-butan-2-one (**2a**): Yield: 67%; $[\alpha]^{27}_{D}$ -36^{0} (*c* = 0.5, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.24 (*s,* 3H), 2.75-2.61 (dd, *J* = 17.9, 9.37 Hz 1H), 3.17-3.08 (d, *J* = 17.9, 1H), 3.76 (*bs*, exchangeable 1H, -OH), 5.68 (d, *J*=9.2 Hz, 1H), 7.39 (t, 1H) 7.62 (t, 1H), 7.92 (m, 2H), ^{13}C NMR (50 MHz, CDCl$_3$) δ 30.8, 51.5, 69.9, 124.8, 128.5, 128.6, 134.2, 138.9, 209.0 ; ESMS *m/z* = 232 (M+Na)$^{+}$; IR (Neat) 3441.6, 1714.2, 1251.7. cm^{-1}. Enantiomeric excess 98%, determined by HPLC (Chiradex column, CH$_3$CN/Water = 90/10), UV 254, flow rate 0.7mL/min. Major; t_R 3.63.

4-Hydroxy-4-(4'-Nitrophenyl)-butan-2-one (**3a**): Yield: 60% ; $[\alpha]^{27}_{D}$ +23 ^{0} (*c* = 0.5, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.22 (s, 3H), 2.83 (m, 2H), 3.69 (bs, exchangeable 1H), 5.27 (m 1H), 7.53 (d, *J*=8.6 Hz , 1H), 8.20 (d, *J*= 8.6 Hz 1H), CH$_3$); ^{13}C NMR (50 MHz, CDCl$_3$) δ 31.0, 51.9, 69.2, 124.0 126.8, 147.5, 150.9, 208.8; FABMS *m/z* = 210 (M+H)$^{+}$; IR (Neat) 3428.4, 1670.1 1209.7. cm^{-1}; Enantiomeric excess 86%, determined by HPLC (Chiradex column, CH3CN/Water = 90/10), UV 254, flow rate 0.7mL/min.; Minor t_R 3.28 and Major; t_R 3.71

4-Hydroxy-4-(4'-floro-phenyl)-butan-2-one (**4a**): Yield: 57%; $[\alpha]^{27}_{D}$ +19^{0} (*c* = 1, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.13 (s, 3H), 2.82 (m, 2H), 3.3 (bs, exchangeable 1H), 5.10 (m, 1H), 7.01 (t, 2H,), 7.29 (m, 2H), ^{13}C NMR (50 MHz, CDCl$_3$ +CCl$_4$) δ 31.0, 52.4, 69.4, 115.4, 115.8, 127.6, 127.7, 139.0, 164.9, 208.7; ESMS *m/z* = 205 (M+Na)$^{+}$; IR (Neat) 3443, 1705.7, 1217.5 cm^{-1}. Enantiomeric excess 76%, determined by HPLC (Chiradex column, CH$_3$CN/Water = 90/10), UV 254, flow rate 0.7mL/min. Minor; t_R 3.39 and Major isomer; t_R 3.55.

4-Hydroxy-4-(4'-Bromophenyl)-butan-2-one (**5**):Yield: 52% ;$[\alpha]^{27}_{D}$ +15^{0} (*c* =0.5, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.19 (s, 3H), 2.82 (m, 2H), 3.42 (d, *J* = 2.8 Hz 1H), 5.11 (m, 1H), 7.25 (m, 2H), 7.47 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 31.1, 52.2, 69.5, 109.9, 127.8, 131.9, 142.5, 209.1; FABMS *m/z* = 241 (M+H)$^{+}$; IR (Neat) 3431.5, 1709.7, 1218.7 cm^{-1}. Enantiomeric excess 3%, determined by HPLC (Chiradex column, CH$_3$CN/Water =80/20), UV 254, flow rate 0.7mL/min. Major; t_R 3.31 and Minor; t_R 3.47

Carbohydr. Res. 341, 2737 (2006)

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