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RAPID COMMUNICATION

Enantioselective aminocatalysis: Michael addition of unactivated ketones to nitroolefins catalyzed by D-fructose derived monofunctional primary amine

KHIANGTE VANLALDINPUIA[a,b], PORAG BORA[a], GRACE BASUMATARY[a], RAHUL MOHANTA[a] and GHANASHYAM BEZ[a,*]

[a]Department of Chemistry, North Eastern Hill University, Shillong, Meghalaya 793 022, India
[b]Department of Chemistry, Pachhunga University College, Aizawl, Mizoram 796 001, India
E-mail: ghanashyambez@yahoo.com

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Abstract. Organocatalytic asymmetric Michael addition is considered among the most extensively studied, yet challenging stereoselective reactions due to the fact that the electrophilic prochiral carbon in Michael acceptor lies away from stereodirecting groups of the catalyst. Although there is a report on stereoselective organocatalysis in Michael addition employing monofunctional secondary amine, the use of monofunctional primary amine for the said reaction is not reported till date. In fact, no monofunctional aminocatalyst is reported yet for the synthesis γ-nitro carbonyl compounds. Here we report our preliminary results on the enantioselective Michael addition of different ketones to nitro olefins catalysed by monofunctional primary amine (**1**) derived from D-fructose.

Keywords. Stereoselective aminocatalysis; monofunctional amine; D-fructose; Michael addition; nitroalkene.

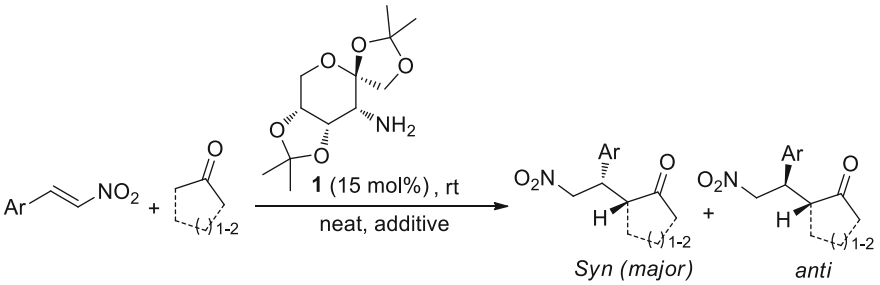
1. Introduction

Organocatalytic asymmetric Michael addition is one of the most extensively studied stereoselective reactions in recent years. The pioneering works of List[1] and Barbas[2] on organocatalytic asymmetric Michael additions have inspired many investigations[3–5] employing multifunctional amine catalysts such as amine-thioureas[6–14] and substituted pyrrolidines.[15–36] Carbohydrate is one of the most enticing class of nature's chiral pools due to their chiral backbone that helps in stereochemical induction. In 2008, Zhou *et al.*, reported the advantage of using bifunctional thiourea organocatalysts derived from α-D-glucopyranose, galactose and lactose for asymmetric Michael addition of acetyl acetone to nitro olefins giving up to >99% yield and up to 96% enantioselectivity.[37] Benaglia *et al.*,[38] used another new class of glucosamine-based bifunctional organocatalysts for nucleophilic Michael addition of acetylacetone to nitro olefins and *N*-Boc imines of benzaldehyde to achieve up to 93% yield and 83% ee. More recently, Peddinti *et al.*,[39] and Shao *et al.*,[40,41] reported organocatalysts derived from α-amino acids and carbohydrates for asymmetric Michael addition in solvent-free conditions. Given the importance of stereoselective Michael addition of carbonyl compounds to nitroalkenes[42] in the synthesis of synthetically useful γ-nitro carbonyl compounds,[43–45] Ma and co-workers reported bifunctional thiourea catalysts prepared from commercially available β-D-glucopyranose for a highly enantioselective Michael addition of aromatic ketones to nitroolefins.[46]

Even though the use of bifunctional amino catalysts is routine, there is only one report on the use of monofunctional amine for the said reaction. Gellman and Chi[47] used diphenylprolinol methyl ether, a monofunctional secondary amine to catalyze intermolecular Michael addition of simple aldehydes to relatively non-activated enones with enantioselectivities up to 99% with catalyst loading of 1–5 mol%. But the method worked best with catechol as a co-catalyst, which was believed to electrophilically activate the enone *via* hydrogen-bond donation to the carbonyl oxygen. Interestingly, stereoselective organocatalysis employing monofunctional primary amine is not reported till date. To our knowledge, no monofunctional aminocatalyst is reported yet for the synthesis γ-nitro carbonyl compounds as well.

*For correspondence

Electronic supplementary material: The online version of this article (doi:10.1007/s12039-017-1371-6) contains supplementary material, which is available to authorized users.



Scheme 1. Michael reaction catalysed by primary amine.

Therefore, we wish to report our preliminary results on the enantioselective Michael addition of different ketones to nitro olefins catalysed by monofunctional primary amine (**1**) derived from D-fructose (Scheme 1).

2. Experimental

2.1 *General remarks*

Chemicals and reagents were purchased from commercial sources and used without further purification. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker AC-400 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, while the elemental analyses of the complexes were performed on a Perkin–Elmer-2400 CHN/S analyzer. Reactions were monitored by thin layer chromatography (TLC). The melting points of the compounds were recorded by open capillary method and were uncorrected. HPLC analysis was carried out on a Waters M515 equipped with Chiracel OD-H and Chiralcel AD-H columns using *n*-hexane and 2-propanol as mobile phase at room temperature.

2.2 *General procedure for Michael reaction*

A mixture of D-fructose derived amine **1** (0.15 mmol), benzoic acid (0.15 mmol) and ketone (4 mmol; 10 mmol in the case of acetone) were stirred at room temperature for 30 min. Nitroolefin (1 mmol) was then added. The reaction was allowed to run at room temperature and the progress of the reaction was monitored by thin layer chromatography. After the reaction was completed, saturated solution of ammonium chloride was added to the reaction mixture and stirred for another 10 min. The compound was extracted with ethyl acetate (3 x 20 mL), washed with water (3 times), dried over Na_2SO_4 and concentrated to get the crude product. The product obtained was further purified using flash column chromatography to obtain the pure Michael adduct.

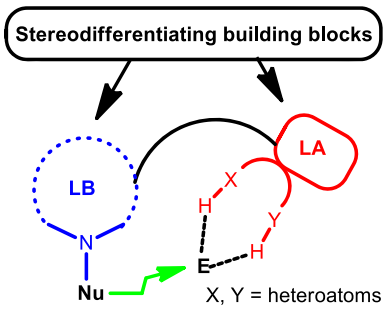


Figure 1. Aminocatalysis with bifunctional amine.

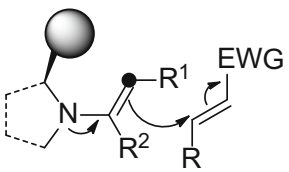


Figure 2. Aminocatalysis with monofunctional secondary amine.

3. Results and Discussions

In continuation of our report[48] on aldol reaction employing D-fructose based amine **1** as organocatalyst, we wanted to extend the application of the catalysts **1–6** for direct Michael addition reactions. It may be noted that unlike aminocatalytic stereoselective Aldol and Henry reactions, where the stereodirecting group binds with carbonyl compound to facilitate the stereoselective 1, 2-addition reaction, the stereodirecting group bound to the Michael acceptor stays away from the electrophilic reaction centre, *i.e.*, the carbon-carbon double bond. As a result, use of bifunctional organocatalysts is an absolute necessity in Michael type addition reaction where both the donor and acceptor molecule bind with the organocatalyst that comprises strategically placed stereodirecting cum activating groups to achieve the desired selectivity (Figures 1, 2).

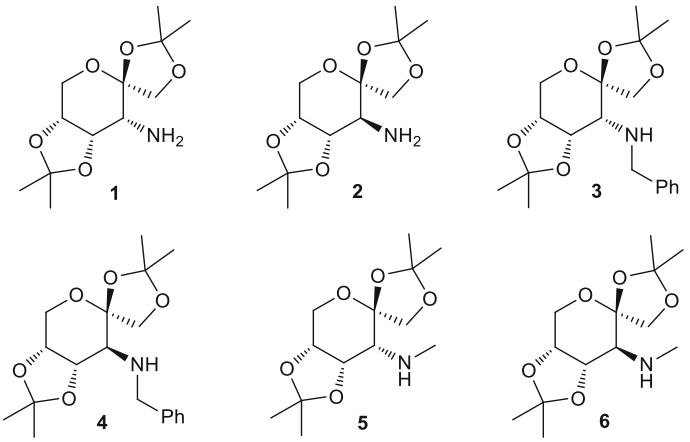


Figure 3. D-fructose derived amines.

Table 1. Solvents effect of asymmetric Michael reaction using sugar derived organocatalysts.

Entry	Catalyst (15 mol%)	Solvent	*t* (h)	Yield %[a]	*dr*[b](*syn*:*anti*)	*ee*[c] *syn*	*anti*
1	**1**	Neat	96	45	77:23	62	21
2	**2**	Neat	96	57	47:53	16	31
3	**3/4/5/6**	Neat	120	Trace	–	–	
4	**1**	CH_2Cl_2	120	21	71:29	47	19
5	**1**	$CHCl_3$	120	Trace	64:36	21	23
6	**1**	DMSO/DMF/CH_3CN/H_2O	120	Trace	–	–	

Reaction condition: *p*-methoxy-β-nitrostyrene (0.2 mmol), catalyst (15 mol%) and cyclohexanone (0.8 mmol).
[a]Isolated yields.
[b]Diastereoselectivity was determined by ^{1}HNMR of the crude product or HPLC analysis of the pure product.
[c]Determined by HPLC analysis.

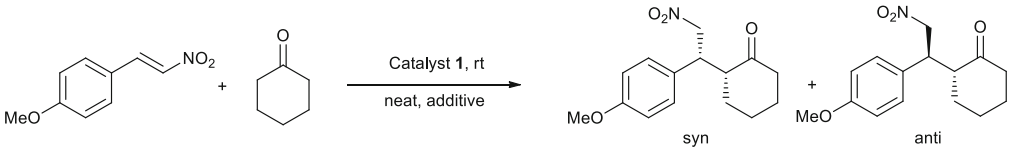
Given the fact that D-fructose based amines **1–6** possess the sugar backbone with two adjacent isopropylidene rings which may control the stereoselectivity of the Michael addition reaction similar to that of diphenylprolinol methyl ether,[47] we screened the catalytic activity and stereoselectivity of the catalysts **1–6** (Figure 3) by taking the reaction of cyclohexanone and 4-methoxy β-nitrostyrene as the model reaction (Table 1). Moderate yield (45%) with moderate diastereoselectivity (77:23 dr) and enantioselectivity (62%) were obtained for *syn* product when the reaction was catalysed by **1** (Table 1, entry 1).

When the model reaction was carried out with catalysts **2** under the neat reaction conditions, Michael product was obtained in 57% yield with 47:53 diastereomeric ratio and 31% *ee* for the *anti* adduct. Consistent with our earlier observations in Aldol reaction, the fructose derived secondary amines **3–6** did not give any product under this reaction conditions (Table 1, entry 3) which led us to conclude that because of high steric congestion in secondary amines **3–6**, the catalysts carrying the primary amine may be more suitable to catalyze the reaction.

A series of solvents were screened (Table 1, entries 4–6) to confirm that the reaction gave the best result in the absence of solvents. Dichloromethane gave the best result among the solvents under scrutiny (Table 1, entry 4) giving 21% yield with 47% *ee* for the *syn* adduct. Although the reaction gave trace amount of the desired product with inferior stereoselectivity in $CHCl_3$, the reaction did not work in other solvents at all (Table 1, entry 6). Catalyst **2** gave better result in term of yield, but the selectivity was rather poor (Table 1, entry 2). Catalysts **3–6** having secondary amine functionality gave only trace amount of conversion even after stirring for 120 h which may be accounted for the high steric crowding around the amine group of the catalysts.

The influences of the amount of catalyst loading and addition of additive on a reaction were then examined. 15 mol% catalyst loading was found to be optimum,

Table 2. Monofunctional amine catalysed Michael addition reaction between cyclohexanone and *p*-methoxy-*β*-nitrostyrene.



Entry	Catalyst **1** (mol%)	Additive	*t* (h)	Yield %[a]	*dr*[b] (*syn*:*anti*)	*ee*[c] *syn*	*ee*[c] *anti*
1	15	TFA	36	67	60:40	33	11
2	15	*p*-TsOH	120	<10	–	–	
3	15	HOAc	72	78	57:43	32	12
4	15	PhCOOH	36	86	88:12	89	65
5	20	PhCOOH	36	86	85:15	84	57
6	10	PhCOOH	48	76	82:18	79	59
7	5	PhCOOH	72	53	83:17	78	51

Reaction conditions: *p*-Methoxy-*β*-nitrostyrene (0.2 mmol), catalyst (15 mol%), additive (15 mol%) and cyclohexanone (0.8 mmol).
[a]Isolated yields.
[b]Diastereoselectivity was determined by ^{1}HNMR of the crude product and validated with HPLC data.
[c]Determined by HPLC analysis.

while its decrease to 5 mol% and 10 mol% negatively affected the reactivity as well as selectivity of the reaction (Table 2, entries 6–7). On the other hand, increasing the catalyst loading to 20 mol% remained essentially the same as that of the reaction catalyzed by 15 mol% of **1**, while the enantioselectivity decreased slightly from 91% *ee* to 84% *ee*. Addition of additives such as TFA, HOAc and benzoic acids greatly enhanced the catalytic performance, probably by accelerating the formation of the enamine intermediate between the catalyst and the substrate. In fact, use of 15 mol% catalyst **1** in the presence of 15 mol% of benzoic acid under solvent free conditions was found to be optimum giving Michael adducts in 86% yield with 88:12 diastereoselective ratio and 89% enantiomeric excess in favour of the *syn* adduct (Table 2, entry 4). It is inexplicable to note that addition of *p*-TsOH deactivates the reaction as it gave the product in less than 10% yield (Table 2, entry 2).

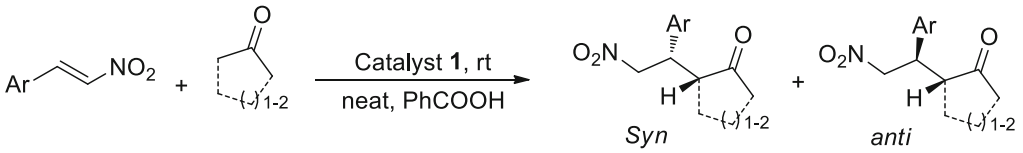
With the optimal reaction conditions in hand, the reaction was carried out on a diverse range of substrates to explore the general applicability of this asymmetric transformation. As shown in Table 3 (entries 1–13), high isolated yields were obtained for all the products, regardless of the electronic nature of the aromatic substituents, and in most of the cases, *syn* products were obtained as the major product with moderate to high enantioselectivities.

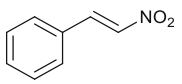
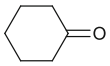
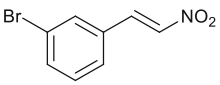
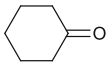
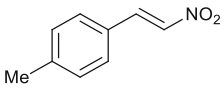
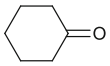
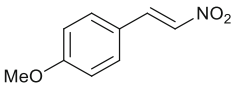
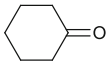
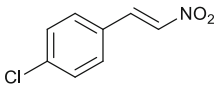
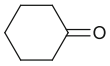
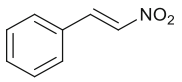
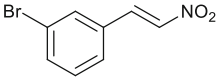
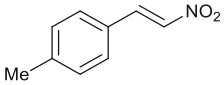
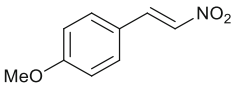
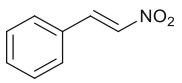
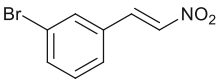
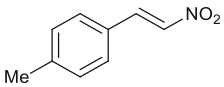
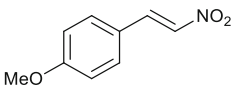
When 1-[(*E*)-2-nitrovinyl]benzene was treated with cyclohexanone and benzoic acid in the presence of D-fructose derived 1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-*α*-D-fructopyranose (**1**) as a catalyst, the product **7a** was obtained in 92% yield after 24 h of stirring (Table 3, entry 1). When the same reaction conditions were applied to the addition of cyclopentanone to nitroolefins the time taken for completion of the reaction was much shorter in comparison to those with cyclohexanone (Table 3, entries 6–9). The reaction of various nitroalkenes with acetone in the presence of catalyst **1** showed excellent conversion with good enantioselectivity, albeit taking longer time than in the cases of cyclopentanone or cyclohexanone.

As far as the plausible mechanism of the reaction is concerned, it may be noted that the secondary amine can bind with carbonyl group to form iminium salt which readily tautomerizes to nucleophilic enamine. On the other hand, unless the enamine form is stabilized by further conjugation, either with an electron-withdrawing group[49] or an aromatic nucleus,[50] or by other less definite stabilizing factors, the reaction of primary amine with carbonyl compound leads to unfavourable imine-enamine equilibrium that prefers the less nucleophilic imine form. Therefore, the use of monofunctional primary amine for stereoselective Michael addition poses considerable challenge with respect to (a) the lack of an activation site and stereodirecting group in the catalyst (Figure 2) for the Michael acceptor which is attacked by the Michael donor, *i.e.*, the imine or enamine generated from the reaction of ketone with the amine catalyst; (b) formation of less reactive Michael donor in the form of imine (Figure 4).

The fact that the reaction of primary amine with carbonyl compound favours the less nucleophilic imine form, we carried out DFT calculation to see the stability of imine and enamine derived from the reaction of cyclohexanone with the catalyst **1**. To our pleasure, it was observed that the enamine form **1b** is more stable by

Table 3. Asymmetric Michael addition reaction catalyzed by **1**.



Entry	Substrate	Ketone	Product	*t*(h)	%Yield[b]	dr[c] syn:anti	%ee[d]
1			**7a**	24	92	69:31	92
2			**7b**	12	95	76:24	76
3			**7c**	30	85	78:22	90
4			**7d**	36	86	88:12	89
5			**7e**	10	96	59:41	78
6			**7f**	7	93	69:31	99
7			**7g**	6	92	60:40	63
8			**7h**	16	90	69:31	47
9			**7i**	20	87	69:31	79
10			**7j**	36	89	-	63
11			**7k**	36	91	-	58
12			**7l**	48	79	-	67
13			**7m**	48	77	-	80

Reaction condition: Nitroolefin (0.2 mmol), catalyst **1** (15 mol%), PhCOOH (15 mol%) and ketones (0.8 mmol).
[a]Isolated yields.
[b]Diastereoselectivity was determined by ^{1}HNMR of the crude product.
[c]Enantioselectivity of the *syn*-diastereomer was determined by chiral HPLC analysis.

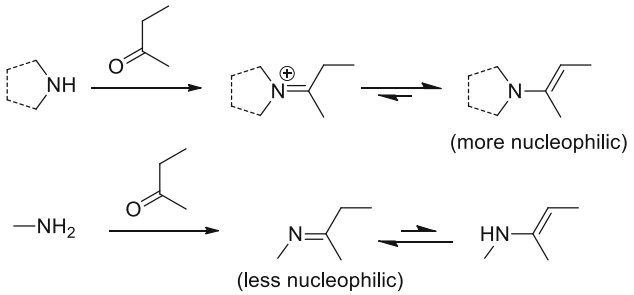


Figure 4. Enamine formation.

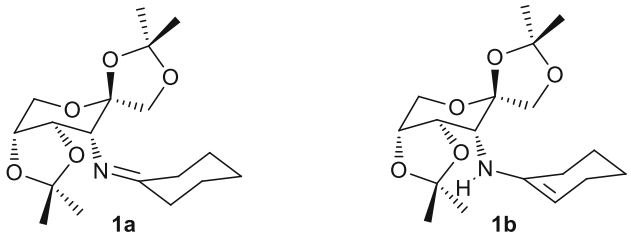


Figure 5. Structure of imine and enamine.

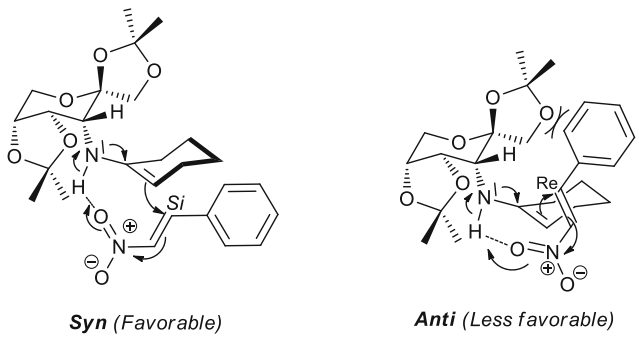


Figure 6. Plausible mechanism of *syn*-selectivity.

0.377 Kcal/mol[51] than the imine form **1a** (Figure 5). The shift in imine-enamine equilibrium to more nucleophilic enamine can be attributed to the lesser conformational restriction in enamine form in comparison to the imine.

As for the plausible mechanism of *syn*-selectivity, a tentative model representing the prototypical addition of cyclohexanone to *trans*-β-nitrostyrene in the presence of organocatalyst **1a** might explain that the NH group of the enamine interacts through hydrogen bonding with the nitrogroup of the nitroalkene and enhances their electrophilicity. The *si*-face approach to the nitroolefin, where the plan of the nitroolefin lies below plane of the enamine, generates *syn*-product while the *re*-face approach to the nitroolefin may be less favourable due steric interaction between the five-membered acetonide ring with the substituent on the β-position of the nitroolefin (Figure 6).

In conclusion, we have reported for the first time a stereoselective organocatalyst having only one activating group in the form of amine for asymmetric Michael addition of ketones to nitroolefins. Given the fact enamine derived from secondary amine is more nucleophilic, the favourable imine-enamine equilibrium in primary amine derived enamine is explained by DFT studies. While the D-Fructose derived primary amine, 1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy- α-D-fructopyranose (**1**) has been found to be an effective catalyst for asymmetric Michael addition of ketones to nitroolefins giving up to 96% yield, 88:12 *dr* and 89% *ee*,while its opposite stereoisomer (**2**) was less reactive and selective under similar reaction conditions. Interestingly, fructose derived secondary amines **3**, **4**, **5** and **6** were found to be ineffective for this transformation which may be due to steric hindrance.

Supporting Information

The spectroscopic data, ^{1}HNMR and ^{13}CNMR spectra of selected compounds, HPLC data and chromatogram, and computational data etc., are available free of charge via the Internet at http://www.ias.ac.in/chemsci.

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