Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. S. Azad, I. A. Khan and A. K. Narula, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB02158A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C6OB02158A

Journal Name

ARTICLE

Organocatalyzed Asymmetric Michael Addition by Efficient Bifunctional Carbohydrate-Thiourea Hybrid with Mechanistic DFT Analysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Chandra S. Azad[a], Imran A. Khan[b]*†, Anudeep K. Narula[a]*†

A series of thiourea based bifunctional organocatalysts having D-Glucose as core scaffold were synthesized and examined as the catalysts for asymmetric Michael addition reaction of aryl/alkyl trans-β-nitrostyrenes over cyclohexanone and other Michael donors having active methylene. Excellent enantioselectivities (<95%), diastereoselectivities (<99%), and yields (<99%) were attained under solvent free conditions using 10 mol % of **1d$_0$**. The obtained results were explained through DFT calculations using B3LYP/6-311G(d,p)//B3LYP/6-31G(d) basic set. The QM/MM calculations revealed the role of cyclohexanone as solvent as well as reactant at the rate determining step imparting 31.91 Kcal/mol of energy towards the product formation.

Introduction

Recently, the process of asymmetric catalysis based on hydrogen bonding has seen an advancement and the use of bifunctional organocatalysts that include a thiourea group and a tertiary amino group has made a substantial impact. This class of organocatalysts acting as the hydrogen bond donors and acceptors, respectively, which facilitates the activation of a nucleophile and an electrophile simultaneously, in a controlled direction, thus leading to the desired stereochemistry[1]. The first example of such type of catalyst has pronounced by Takemoto. The necessary structural feature of the catalyst was well explained by the Takemoto et al as illustrated in the figure **1**[1c-e].

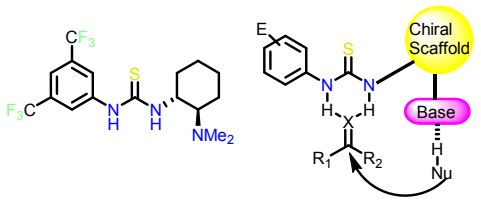


Figure 1. Takemoto catalyst and its prototype.

[a] "Hygeia" Centre of Excellence in Pharmaceutical Sciences (CEPS), GGS Indraprastha University, Sec. 16-C, Dwarka, New Delhi, 110078, India. E mail: aknarula58@gmail.com
[b] Department of Chemistry, Guru Nanak Dev University, Amritsar, Punjab, 143005, India. E mail: imrankhan090@gmail.com
† These authors contributed equally.

Electronic Supplementary Information (ESI) available: The experiment detail of the synthesized catalysts, ^{1}H, ^{13}C, ^{19}F and HPLC data of catalyst and Michael product, values of thermochemical and DFT calculations are added in ESI. See DOI: 10.1039/x0xx00000x

After accessing the importance of chiral scaffolds described by Takemoto, several research groups used the different chiral templates e.g. 1,2-diamino cyclohexane[1c-e], binaphtyl[2a,b], cinchona alkaloids[2c-f], and amino acids[2g]. Only limited chiral templates/scaffolds have been used for the synthesis of bifunctional organocatalysts because of complex synthetic manipulation in addition to cost effectiveness. Whenever discussing the need of chiral templates it is hard to ignore the importance of carbohydrates. The carbohydrate could be consider as chiral template for chiral catalyst like Takemoto's one because of their conformational stability and the presence of distinct spatial arrangement of substituent and various hydroxyl groups[3].

The first example of urea moiety containing carbohydrate based bifunctional organocatalysts containing D-glucosamine scaffold have been described by Kunz et al[4]. Whereas later on Ma et al described the thiourea based bifunctional organocatalysts consisting of monosaccharide and primary amine moieties for the enantioselective Michael addition[5]. Several monosaccharides containing chiral thiourea/urea–amine compounds as bifunctional organocatalyst for stereoselective Michael additions and aza-Henry reactions have been reported[6]. In most of the findings related to monosaccharides containing chiral thiourea-amine compounds as bifunctional organocatalysts, the chiral 1,2-diamino cyclohexane or enantiopure diamine scaffolds were retained for controlling stereochemistry of the reaction, while saccharide have been introduced only as a supplementary scaffold probably beneficial for a tuning of the organocatalyst. To the best of our knowledge, only two reports are published, in which bifunctional thiourea-amine organocatalysts with monosaccharide as a core scaffold have been used for Michael and Henry reaction with enantiomeric excesses ranging from

View Article Online
DOI: 10.1039/C6OB02158A

12.9 to 18.7 % (in 24h)[7a] and from 7 to 20 % (in 72-720h)[7b] respectively.

From the literature available and endeavour towards exploring carbohydrate chemistry [6, 8] an attempt was made to synthesize a new type of thiourea–amine organocatalysts where both catalytic residues were linked by an enantiomerically pure carbohydrate centred scaffold, as a substitute of chiral skeleton to 1,2-diamino cyclohexane. The two type of organocatalysts were designed (i) the -CH2- (n=1) bearing organocatalysts based on the results published by Tang et al[9a] designated as subscript 1 (ii) and rigid analogue (n=0) based on Takemoto design [9b] as subscript 0 (Figure **2**).

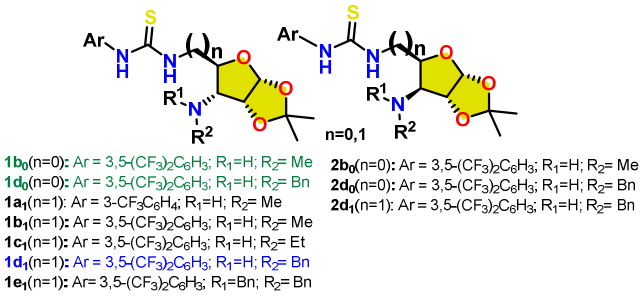
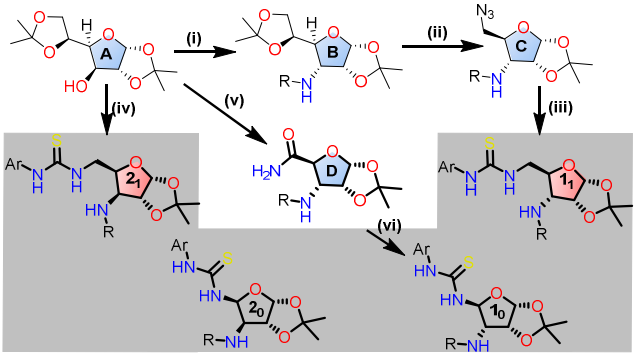


Figure 2. Schematic representation of synthesized catalyst.

Results and discussion

The synthesis of series 1_1 (subscript 1 stand for n=1, Figure 2) was carried out by the conversion of D-glucose into its diacetonide (**A** in scheme 1) with acetone using phosphoric acid as catalyst. The C-3 hydroxy of glucose diacetonide was triflated and subsequently replaced by azide with inverted stereochemistry. The C-3 azide was reduced with LAH and alkylated with the suitable alkylated reagent (**B** through condition **i** in scheme **1**). The C-5,6 protection is cleaved by acetic acid and diol so formed upon periodate oxidation gave aldehyde which was reduced without purification to generate C-4 primary alcohol. The C-4 alcohol is mesylated and subsequently azidated with NaN_3 in DMF (**C** through condition **ii** in scheme **1**). The azide so formed was reacted with aryl isothiocyanate in presence of PPh_3, in which azide reduced *in situ* and led to the formation of thiourea linkage (**1$_1$** through condition iii in scheme **1**).

In the synthesis of 1_o (n=0) series, the authors proposed to descend the catalyst by one carbon for which same reaction sequence was repeated (condition **i**, scheme **1**) upto C-3 amine alkylation and then C-5,6 linkage was cleaved with acetic acid and then diol was oxidative cleaved with sodium periodate, the aldehyde so formed was oxidized with freshly prepared silver oxide to get the N-alkylated sugar amino acid. The acid was converted to the corresponding acid chloride with oxalyl chloride in DCM. This acid chloride was left over night in methanolic ammonia in which amide was formed in good yield (**D** through condition **v** in scheme **1**). The best method to descend the carbon in the amide is the Hofmann rearrangement, in which amide is converted into amine with the loss of one carbon. The reaction conditions reported by by the Ochiai *et al*, were screened, nevertheless the amine in lesser yield was formed. The multispot reaction observed on TLC plates was ascribed to the use of HBF_4[10a], however the use of [bis(trifluoroacetoxy)iodo]benzene [$PhI(CF_3COO)_2$] improved the formation of amine in good yield[10b,c]. The crude amine was further treated with aryl isothiocyanate to yield the desired bifunctional organocatalsyt (**1$_0$** through condition **vi** in scheme **1**). After getting trans 1 series we synthesized the cis 2 series catalysts in which C-3 hydroxy of the glucose diacetonide was flipped with oxidation reduction method[16].Tthe other step of the reaction were the same as in the synthesis of catalyst 1 series (Scheme **1**) (For detailed synthetic procedure see ESI).



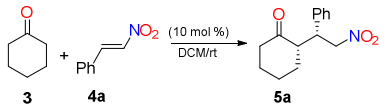
Scheme 1. The synthesis of Glucose based organocatalysts and reaction conditions. (i) (a) Tf_2O, DCM, 0°C, 5h, 95% (b) NaN_3, DMF, 50°C, 8h, 68% (c) $LiAlH_4$, THF, 0°C, 5h, 76% (d) RX, NaH, Dry DMF, 0°C-rt. 12h, (90 % mono alkylated, 24 % di Bn) (ii) (a) 60 % AcOH, 50°C, 4h, 99 % (b) $NaIO_4$, THF:Water (1:1), rt, 1h, 90% (c) $NaBH_4$, MeOH, rt, 10h, 95% (d) MsCl, TEA, DCM , rt, 12h, 99% (e) NaN_3, DMF, 80°C, 12h, 93% (iii) ArNCS, PPh_3, THF, 0°C-rt, N_2 balloon, 12h, 72% (iv) (a) PCC, Ac_2O, DCM, rt-relux, 3h, 89% (b) $NaBH_4$, MeOH:Water (1:1), rt, 3h, 80% then same sequence of reaction as applied for **1$_1$** (v) (a) Tf_2O, DCM, 0°C, 5h, 95% (b) NaN_3, DMF, 50°C, 8h, 66% (c) $LiAlH_4$, THF, 0°C, 5h, 75% (d) RX, NaH, Dry DMF, 0°C-rt. 12h, (92 % mono alkylated, 44 % di Bn) (ii) (a) 60 %AcOH, 50°C, 4h, 95% (b) $NaIO_4$, THF:Water (1:1), rt, 1h, 88% (c) aq $AgNO_3$, KOH, rt, 1h, 75% (d) $COCl_2$, DCM, 0°C, 5h, 54% (e) Methanolic ammonia, 0°C-rt, 12 h, 82% (vi) (a) $PhI(CF_3CO_2)_2$, ACN–H_2O (1:1), rt, 4 h, 42% (b) ArNCS, THF, 0°C-rt, N_2 balloon, 12h, 44%.

After getting designed carbohydrate based bifunctional organocatalysts in hand, the catalytic activity was studied on conjugate addition reaction. The asymmetric Michael addition [1a,11] involving α–enolizable ketones to electron deficient nitroolefins, received attention after first reported by List and Barbas, independently [11d,e]. These reactions led to the formation of γ-nitro carbonyl compounds, found to be important building blocks in organic/medicinal chemistry[12]. Several examples are available till date in which aromatic nitroolefines were used [6g,13] nevertheless reaction of alkyl nitroolefins with cyclohexanone are few,[9a,14] this may be due to the less reactivity of than alkyl nitroolefins then aryl nitroolefins. So cyclohexanones and alkyl/aryl nitroolifines were chosen as model substrates. The screening of the reaction was carried using cyclohexanone (**3**), trans-β-nitrostyrene (**4a**) and 20 mol % of synthesized catalyst in DCM for 24h. As, given in table **1**, yield and enantioselectivity toward the formation of **5a** varied significantly. The catalyst with one CF_3 substitution failed to catalyse the reaction as traces of product were noticed over the

View Article Online
DOI: 10.1039/C6OB02158A

TLC plate (Table **1**, Entry **1**), revealing the necessity of two CF_3 groups on aromatic ring. The C-3,4 trans catalysts (**1b$_1$** and **1c$_1$**) with methylene at C5 carbon found to be active and increasing the size of alkyl group at C3-amine led to the decrease in yield (Table **1**, entries **2** and **3**), although increased in syn/anti ratio and enantioselectivity was noticed. Inspired form these results benzyl as another substrate was considered as it may produce facial hindrance with lesser bulky environment at amine. This resulted in the formation of product **5a** in 52 % yield with 73 % enantiomeric excess (Table **1**, entry **4**). The *N, N* di alkylated catalyst **1e$_1$** failed to produce the **5a** in good yield and enantioselectivity (Table **1**, entry **5**) may be due to steric problem. In the next approach it was proposed to cut off the C5 methylene because it was envisaged that the flexible nature of this $–CH_2-$ would be responsible for decrease in yield and enantioselectivity. As expected the rigid catalyst **1d$_0$** served the purpose and **5a** was formed in 68 % yield with 88% enantiomeric excess (Table **1**, entry **6**). The necessity of Bn over the C-3 amine was cross checked by putting Me instead of Bn and that again led to inadequate results (Table **1**, entry **7**). This showed the importance of Bn in the synthesized catalyst. Although *trans*- symmetry is suggested in between thiourea and base in prototype of Takemoto catalyst, nevertheless cis-symmetry catalyst was also screened, which was hypothesized on the basis of study published by Fugedi *et al.*[7a]. The catalyst **2d$_0$**, **2d$_1$** and **2a$_0$** gave poor results as maximun 25% enantiomeric excess was achieved with 63 % yield (Table **1**, entries **8-10**). Form the above results **1d$_0$** was selected as the catalyst of choice.

Table 1. Screening of catalyst selectivity on the Reaction of Cyclohexanone to trans-Nitrostyrene[a]



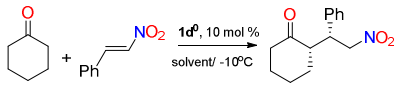
3 4a 5a

Entry	Catalyst	Yield	Syn/anti[b]	ee[c]
1	**1a$_1$**	trace[d]	---	----
2	**1b$_1$**	28	76/23	42
3	**1c$_1$**	23	80/20	52
4	**1d$_1$**	52	95/5	72
5	**1e$_1$**	34	60/40	15
6	**1d$_0$**	**68**	**95/5**	**88**
7	**1b$_0$**	52	90/10	75
8	**2d$_1$**	53	55/45	23
9	**2d$_0$**	63	75/25	25
10	**2a$_0$**	<10	--[e]	---

[a] All reactions were carried out in DCM (5 mL for 1 mmol of cyclohexanone) using 3 (5 equiv) and 4 (1 equiv) in the presence of 10 mol % of catalysts for 24h. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] Anlysed by TLC only. [e] Not determined.

From the results obtained by initial screening (Table **1**), the improvement in the yields was assumed on the basis of basicity of C3 *sec*-amine of sugar counterpart. The *sec*-amine in designed catalyst was not that much sufficient and increasing electron donating groups may reduce the yield due to steric hindrance (Table **1** entry **5**), so it was predicted that adding external base would increase the yield and selectivity. The screening of some common bases like bicarbonate, carbonate, and pyridine, likewise disappointed (Table **2** entries **1-2**). The hindered bases like DABCO, DBU and *i*Pr_2NH gave the desired product **5a** in maximum 72% yield with 62% enantiomeric excess (Table **2**, entries **4-6**). The use of *i*Pr_2NH suggested the use of Et_3N and in 20 mol % of the same, the significant improvement of the yield and enantioselectivity was noticed (Table **2** entry **7**). After getting 92% yield of the desired compound the impact of reaction medium was also evaluated and it was established that reaction medium influenced the process. The most commercial available solvents are attuned with optimized asymmetric conditions and afforded excellent yields (<92%) with excellent to good diastereoselectivities (up to 96:4) and diverse enantioselectivities (Table **2**, entries **7**−**16**). When the reaction was performed in halogenated solvents, e.g. DCM, DCE and $CHCl_3$, excellent diastereoselectivities (< 95/5) and good enantioselectivities (<86%) were obtained (entries **7-9**). The reaction in polar solvents, such as THF, Et_2O, ACN and

Table 2. Screening of base, solvent and catalyst loading on the Reaction of cyclohexanone to trans-nitrostyrene by 1d0*



3 4a 5a

Entry	Base	solvent	Yield	syn/anti	ee
1	$NaHCO_3$	DCM	----	-----	-----
2	Na_2CO_3	DCM	23	95/5	52
3	Pyridine	DCM	43	92/8	48
4	DABCO	DCM	26	60/40	42
5	*i*Pr_2NH	DCM	72	93/7	62
6	DBU	DCM	32	85/15	56
7	Et_3N	DCM	92	90/10	86
8	Et3N	DCE	86	95/5	84
9	Et3N	$CHCl_3$	72	85/5	86
10	Et_3N	THF	54	93/3	72
11	Et_3N	Et_2O	48	96/4	54
12	Et_3N	ACN	32	92/8	62
13	Et_3N	DMSO[a]	44	86/14	49
14	Et_3N	MeOH[b]	18	92/8	22
15	Et_3N	Benzene	77	91/9	69
16	Et_3N	Toluene	82	94/6	76
17	Et_3N	neat[c]	92	94/6	90
18	Et_3N	neat[d]	96	95/5	88
19	Et_3N	neat[e]	94	96/4	91
20	Et_3N	neat[f]	68	94/6	80
21	**Et_3N**	**Neat[g]**	**98**	**99/1**	**94**

*Unless otherwise noted, all reactions were carried out at rt for24h using 10 mol % **1d^0**. [a] Reaction time was 36 h. [b] Reaction time was 2 days. [c] The 25 equiv of cyclohexanone was used. [d] With 30 mol %. [e] With 10 mol %. [f] With 5 mol%. [g] Reaction performed at -10°C for 2.5 days.

DMSO, yielded the **5a** with relatively lower enantioselectivities (entries **10-13**). The adverse effect of the solvent polarity was clearly verified, when reaction performed in the protic solvent like MeOH, poorly yielded the **5a** (Table **2**, entry **14**). When the reaction was carried out in hydrocarbon solvents, product **5a**

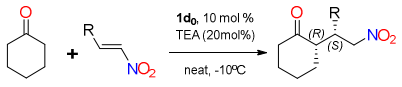
View Article Online
DOI: 10.1039/C6OB02158A

was formed good yield with significant loss of enantioselectivity (Table 2, entries **15** and **16**). The excellent result was obtained when reaction was carried out devoid of any solvent with 25 equivalent cyclohexanone (entry **17**). Additional catalyst loading screening suggested the 10 mol % was sufficient to catalyze he reaction (entries **18-20**). The temperature also showed the effect on the reacting and it was found that lowering the temperature enhanced the yield with slightly increase in selectivity at the cost of reaction time. The optimized temperature was found -10°C, which can easily be achieved by ice salt. The required ratio of Et_3N was also screened and 20% found to be optimum.

Under the optimized condition (entry **21** table **2**), a variety of substrates were studied, and the corresponding products were formed in moderate to high yields with high diastereoselectivities (up to 99:1) and excellent enantioselectivity (up to 95% ee) (Table **3**). In addition to the phenyl, electron rich and electron deficient aryl groups, hetero-aromatic and aliphatic substituents were well tolerated under the optimized reaction condition. The trans-β-nitrostyrene with electron-withdrawing groups gave slightly higher yields than those with electron-donating groups and substituents on aryl groups slightly influenced the diastereoselectivities and enantioselectivities. Although sterically demanding substrates are also well tolerated in this reaction, nevertheless higher reaction time was required to complete the reaction (Table **3**, entries **4**, **7**, **8**, **11**). The alkyl nitroolefins also gave good results (entries **14** and **15**). Additionally, alkenyl substituted nitroolefin also effectively employed offering high diastereo- and enantioselectivity as those found in the aryl substituted ones (entry **16**). The absolute configuration of the major isomer was recognized by comparison of optical rotation in the published literature as described in ESI†.

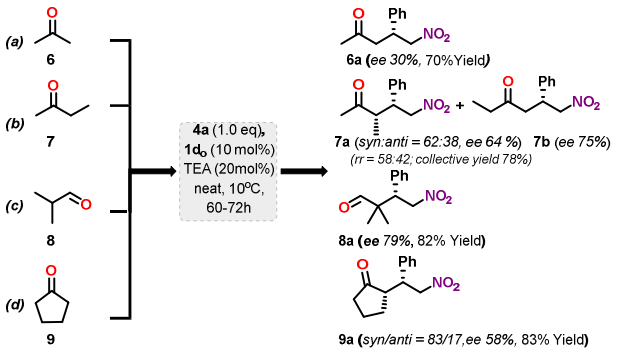
The result so obtained, fortified us to explore the scope of the reaction on other ketones and aldehydes. The acetone and methyl ethyl ketone yielded the desired products in 70 and 78 % respectively, nevertheless in case of unsymmetrical ketone (Scheme **2**, entry **b**) two products were formed in which the lesser substituted enol based product was formed in excess with moderate enantiomeric excess (<75%) but poor regioselectivity. The isobutyraldehyde also showed good results as desired product was formed in 82 %yield with good *ee* (79%) (Scheme **2**, entry **c**). The reaction of cyclopentanone with **4a** under similar reaction condition offered the desired products in 83 % yield with 58% *ee* (Scheme **3**, entry **d**), whereas in the case of cycloheptanone multiple products were obtained, in which self-condensed product predominates as analysed by NMR spectroscopy.

Table 3. Substrate scope of $1d_0$ catalyzed asymmetric Michael addition of cyclohexanone to trans-β-nitrostyrene[a]



Entry	R	time (h)	Yield[b]	syn/ anti[c]	ee[d]
1	Ph (**4a**)	60	98	99/1	94
2	1-Naphthyl (**4b**)	60	92	95/5	94
3	4-MeC_6H_4 (**4c**)	66	89	96/4	87
4	2-$CF_3C_6H_4$ (**4d**)	72	94	98/2	90
5	3-$CF_3C_6H_4$ (**4e**)	60	92	94/6	91
6	4-ClC_6H_4 (**4f**)	66	96	95/5	94
7	2-NO_2-5-ClC_6H_3 (**4g**)	78	95	96/4	93
8	2-$NO_2C_6H_4$ (**4h**)	72	94	93/7	91
9	Benzo[d][1,3]dioxol-5-yl (**4i**)	60	91	94/6	95
10	4-$MeOC_6H_4$ (**4j**)	66	86	93/7	93
11	2,4-$(MeO)_2C6H_3$ (**4k**)	84	88	92/8	88
12	2-Furyl (**4l**)	60	90	94/6	91
13	2-Thienyl (**4m**)	60	85	98/2	92
14	*iso*-propyl (**4n**)	72	62	96/4	92
15	*iso*-butyl (**4o**)	78	58	80/10	90
16	(E) cinnamyl (**4p**)	60	72	95/5	89

[a] All reactions were carried out using **3** (25.0 equiv.) and **4** (1.0 equiv.) in the presence of 10 mol % of $1d_0$ and 20 mol % of TEA in neat at -10°C. [b] Isolated yield. [c] Determined by ^1H NMR of the products. [d] Determined by chiral HPLC analysis.



Scheme 2. Reactions of other ketones and Aldehyde.

For extending the substrate scope of the reaction, authors examined the Michael reaction of β-nitrostyrene with other Michael donors *viz.* 1,3 dicarbonyl, 1,3 dicyano, β-keto esters and α-cyano esters. The results are summarized in Table **4**. Under optimized condition, upto 95 % yield with 96% enantioselectivity was obtained even without the use of TEA. The stereochemical outcome of the reaction was found to be significantly influenced by the structure of the Michael donors. The sterically more hindered donors readily reacted with nitrostyrene in presence of $1d_0$ to give the corresponding adduct in higher *ee* and yield (entries 6, 7 and 9, 11, table 4). The β-keto esters showed the excellent diastereoselectivity as methyl 3-oxobutanoate and ethyl 3-oxobutanoate gave 96:4 and 92:8 diastereoselectivity respectively (entries 9 and 10, table 4), while in case of α-cyano ester less than 5% of diastereoselectivity was observed (entry 11, table 4). The Michael adducts so formed noticeably showed the applicability of the optimised methodology on the wide range of substrates. The optimized method can be utilized for the synthesis of

View Article Online
DOI: 10.1039/C6OB02158A

enatiopure Baclofen, Rolipram, and Femoxitine drug molecules in good *ee* using published literature [9b,15] (Figure **3**).

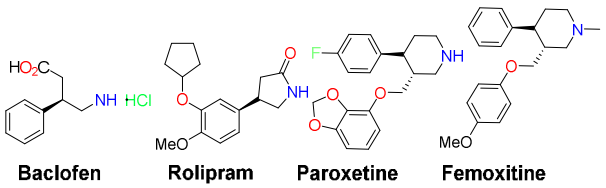
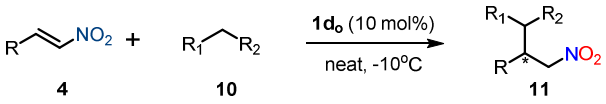


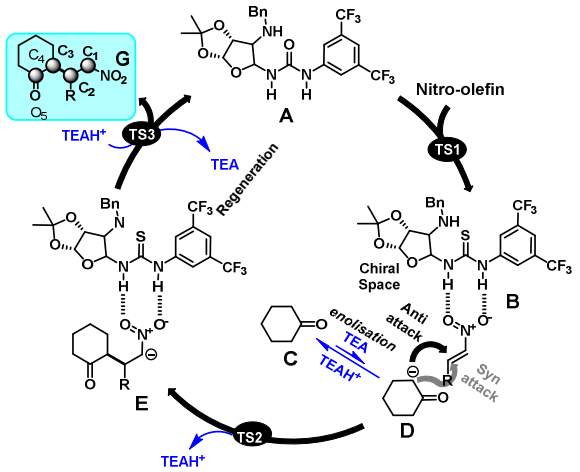
Figure 3. The drug candidates which can be synthesized by devised methodology.

Table 4. Enantioselective Michael reaction of nitroolefins with Michael donors in the presence of $1d_0$[a]



Entry	Nitroolefins	Michael donor	Time (h)	Yield (%)[b]	ee[c] (Config)[d]
1	4a	R_1=R_2=CO_2Et	66	95 (11a)	94 (R)
2	4c	R_1=R_2=CO_2Et	78	92 (11b)	92 (R)
3	4f	R_1=R_2=CO_2Et	78	85 (11c)	89 (R)
4	4m	R_1=R_2=CO_2Et	60	93 (11d)	92 (S)
5	4o	R_1=R_2=CO_2Et	84	84 (11e)	85 (S)
6	4a	R_1=R_2=COMe	96	91 (11f)	82 (S)
7[e]	4a	R_1=R_2=COEt	60	95 (11g)	96 (S)
8[e]	4a	R_1=R_2=CN	72	88 (11h)	92 (R)
9	4a	R_1=COMe; R_2=CO_2Me	87	92 (11i) *dr* 96:4[f]	94[g]
10	4a	R_1=COMe; R_2=CO_2Et	92	95 (11j) *dr* 92:8[f]	96[g]
11	4a	R_1=CN; R_2=CO_2Me	90	78 (11k) *dr* < 5%[f]	72[g]

[a]The reaction was carried out with 1 equiv. of **4** and 10 equiv. of Michael donor in the presence of 10 mol% of catalyst at -10°C. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC. [d] Absolute configuration was determined by comparing the optical rotation with published literature. [e] Reaction was performed in the presence of 4 ml of DCM per 1 mmol of **4**. [f] Determined by ^{1}H NMR of the products. [g] Not assigned.



Scheme 3. Mechanistic insight of the reaction Michael addition reaction of aryl/alkyl trans-β-nitrostyrenes over cyclohexanone

To explain the stereochemical outcome of the reaction, computational studies were performed. All theoretical calculations were performed using the Gaussian 09 program package. Density functional theory (DFT), which has been proved to be a powerful tool for the study of reaction mechanisms, was chosen in this computational work[16].

Considering the complexity of the theoretical model used for this study, all the structural optimizations were carried out at the B3LYP-6-311g(d,p)/6-31G(d,p) level in gaseous condition at 263K, Additionally, the structures (local minima or first-order saddle points) were located by performing full geometry optimization. Then the corresponding vibrational frequencies were calculated at the same level to take account of the zero-point vibrational energy (ZPVE) and to identify the transition states. It was confirmed that all the reactants, reaction precursors, intermediates, and products had no imaginary frequencies, and each transition state had only one, imaginary frequency. Intrinsic reaction coordinate (IRC) calculations at the same level were performed to verify that each saddle point links two desired minima and the transition states led to the expected reactants and products. Based on the optimized structures, the single-point energies were further refined using the 6-311+G(d,p) basis set in gaseous phase. All discussions in this manuscript are based on the Gibbs free energies. According to DFT studies, the possible catalytic mechanism for the title reaction is depicted in Scheme **3**. The reaction mechanism can be divided primarily in four parts after the formation of the adduct; (i) Formation of thiourea-nitrostyrene (**TU**-**NS** adduct) complex (**B**); Activation of the ketone through TEA (**C** to **D**); (ii) the Michael addition (**D**); (iii) proton abstraction from the $TEAH^+$ resulting to the formation of **E**; and (iv) regeneration of catalyst (**A**) (Scheme **3**).

The first step of the reaction in mechanism is the combination of TEA with cyclohexanone and formation of cyclohexanenolate ion (**Scheme 3**) and simultaneously the formation of stabilized octa membered hexagonal adduct between Nitrostyrene and 1-((3a*R*,5*S*,6*S*,6a*R*)-6-(benzylamino)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (**$1d_0$**) formed by the strong hydrogen bond interactions. The optimized structure of adducts (**Fig 4** in **ESI**) formed with the inversed stereochemistry at the C3 of the sugar part was found to be more thermodynamically stable than the naturally occurring stereoisomer. A weak hydrogen bond was found to be formed between sulfur of **TU** and NH of sugar at C3 which was not found favorable in case of normal isomer based **TU** catalyst. This showed the greater favorability of adduct (**B**) for the Michael addition in the fate giving 3*S*, 17*R* product which directly proved the formation of SR product as the favorable due the decrement of the p-character of the bond as suggested through the output files. The NBO studies revealed that shortened C1(α)=C2(β) (NS) in adduct was assisted with change in NBO charge from 0.08e and 0.06e to 0.015e and 0.06 in **Fig 3 (ESI)** and 0.017e and 0.09 **Fig 4 (ESI)**, showed a slight decrement of *p* characters is imparted by TU (both normal and inverted forms) to the Michael acceptor site. Obviously, polarization of NS in this step, indicated the catalyst to be the Lewis base organocatalyst. The energy barriers of the first step were 26.0 kcal mol^{-1}

View Article Online
DOI: 10.1039/C6OB02158A

(associated with normal-configuration **TS1** (*anti*), **Fig. 7** in **ESI**) and 9.9 kcal mol^{-1} (associated with **TS1** (*syn*), **Fig. 21** in **ESI**). The second step in mechanism is the formation of three hydrogen bond governed intermediate with (O•••N Ar; O•••N sugar; O enolate•••N terminal). In this step, the reaction precursor (**Fig 8** in **ESI)** undergoes the Michael addition transition state **TS2**. There were four different kinds of stereoisomer, i.e. *SS*, *SR*, *RS*, and *RR* configurations, in this addition process. As shown in figure **4** the energy barrier *via* **TS2** (SS, RR, SR & RS) is -63.01/-63.00/-75.13/-60.97 kcal/mol, indicating the pathway associated with stage 4 (SR) had the lowest energy barrier among the four competing fates, thus, it should be the most favorable pathway and the *SR* configuration would be the favorable stereoisomer; this was in agreement with the experiment. Accompanied with the formation of bond C3–C4, the single bond C4–O5 was also generated subsequently in step involving conversion to **TS3** from **stage 5** (*SS, RR, SR &RS*) *via* **TS2** (*SS, RR, SR & RS*), so the addition is a concerted process. Where the distances between C2–C3, and O5–C2 in **TS2** and **TS3** (*SS*, *RR*, *SR & RS*) decreased, whereas the distances C3–C4 and C4–O5 are increased in this process. As depicted in scheme **3**, the different stereoselectivities associated with the chiral carbon centers C3 and C4 were generated in the addition process, so envisaged that the stage VI could be the key for the stereoselectivity. In addition, the difference of the energy barrier between *SR* and *RS* configurations in this stage is 5.89 kcal/mol; this value correspond to an enantiomer excess of 95%, which was s to our experimental outcome (94% *ee*). The benzene ring of the nitro styrene and phenyl group of the catalyst were 3.41 Å apart in **TS2** which signifies the π–π weak interaction be the driving force for the formation of **P** (***RS***), whereas the same distance is 3.65 Å at **TS2** for the formation of the ***SR*** product. Therefore, a weak π–π interaction, leads the reaction to the observed stereochemical preference. The conformational arrangement at sugar moiety which favors the SR product formation could be explained through the spontaneous formation of **TS2** and **TS3** supported through the free energy (ΔG_{SR}>ΔG_{SS}>ΔG_{RS} >ΔG_{RR}) and in the case of TS2 the steepness in IRC curve for the SS conformation thus decreases the favourability (IRC3, ESI).

In the last step of mechanism, the catalyst and product (*SS, RR, SR & RS*) dissociated by breaking the N-O•••H-N bond through transition state **TS3** (*SS*, *RR*, *SR & RS*), the change of the distances N-O•••H-N reflects the nature of this reaction process. The distances N-O•••H-N are increased to 2.043/2.045/2.011/2.090 Å in **TS3** (*SS, RR, SR & RS*), respectively. The energies of product (*SS*, *RR*, and *SR & RS*) in presence catalyst were found to be lower than those of the

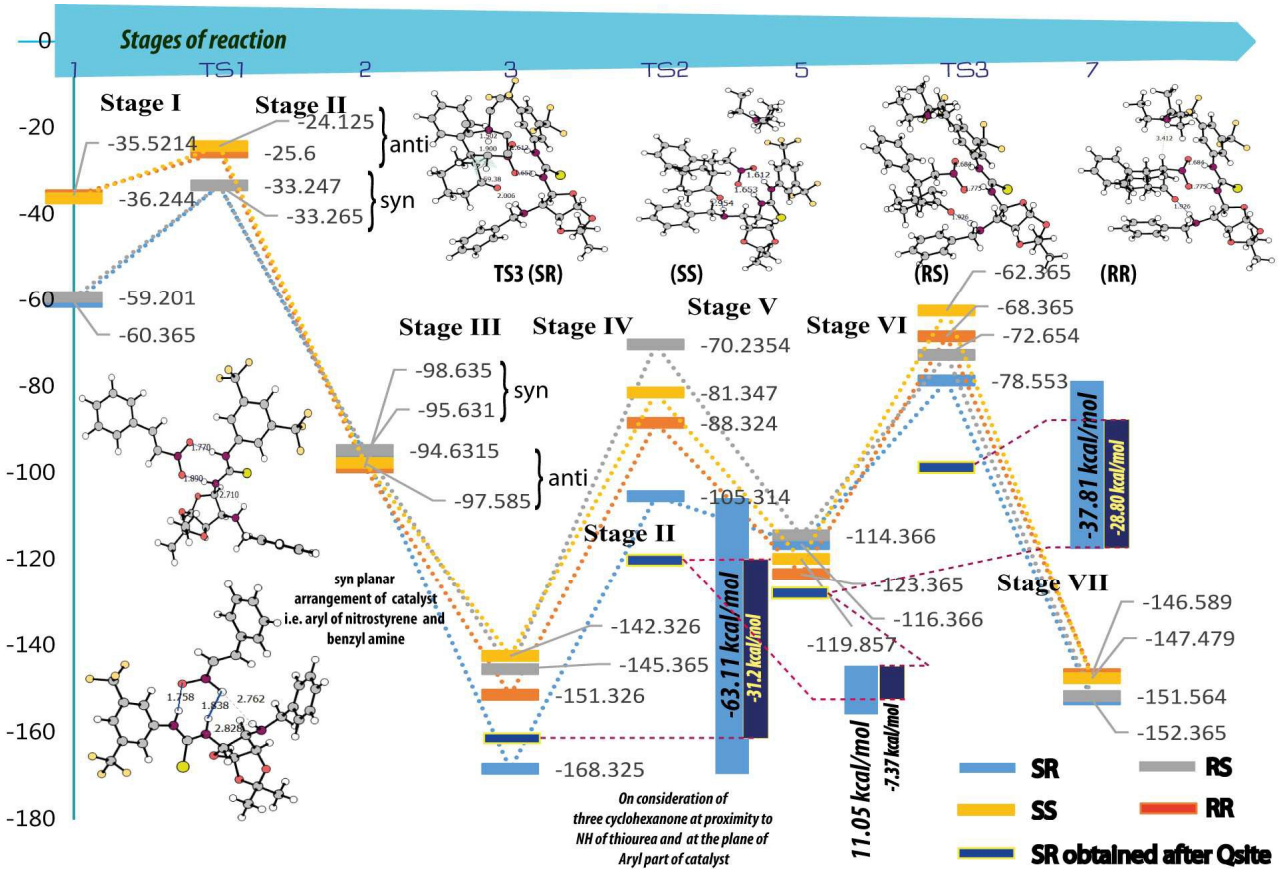


Figure 4. Energy (E+ ZPVE) profile of the possible reaction mechanism. Numbers in parentheses are relative Gibbs free energies (unit: kcal mol^{-1}). The Gibbs free energies of NS+ R2+ thiourea+TEAH$^+$ was set as references (0.0 kcal/mol); the notations SR, SS, RS and RR stands for the stereochemistry at C2 from NO_2 and C2 from C=O of NS and cyclohexanone respectively.

View Article Online
DOI: 10.1039/C6OB02158A

reactants respectively, indicating the overall reaction is an exothermic process. Furthermore, the energy barrier via **TS3** (*SS, RR, SR* & *RS*) was found to be -51.492/-50.712/-37.813/-41.712 kcal/mol, this suggested that the third step should be also a slow process. The larger energy gap at stage IV and VI were seen unfavorable due to the non-consideration of the cyclohexanone in excess as it was envisaged that cyclohexanone played role as solvent. Therefore, to justify the role of solvent molecular dynamic calculation for the system resulting were carried out which resulted the formation of product with *SR* configuration using Desmond in Schrondinger[17]. The obtained system after MD equilibriums (4ns) was subject under QM/MM calculations using the Qsite protocol with B3LYP/6-311g and RHF/631g basis set for the high layer and low layer respectively. The obtained results showed lowering in the relative energy gap from 72 kcal/mol to 31.2 kcal/mol at stage IV and 37.81 kcal/mol to 28.80 kcal/mol at stage VI depicting three more cyclohexane molecules around the reactants (Figure 35, 36 in ESI). The execution of similar studies was avoided due to the high computational cost.

Conclusions

In conclusion, we developed an efficient carbohydrate core scaffold having thiourea and *sec*-amine group, which worked excellent as a bifunctional organocatalyst to carry out the asymmetric Michael reaction of cyclohexanone and Michael donors to both aryl and alkyl nitrooelfins. In the current finding, the designed and synthesized catalyst showed a high catalytic activity, and reaction was completed with excellent diastereo (up to >99%) and enantioselectivity (up to 95 % *ee*), which may be further useful for the synthesis of β-nitroketones. The devised methodology may find a use in the synthesis of some chiral drugs *e.g.* Baclofen, Rolipram, Paroxetine and Femoxitine with good enantioselectivity. The plausible explanation to the enantioselectivityis supported through computational calculation using density function theory in Gaussian 09.

Experimental

General reaction condition for the Michael addition of ketones to Nitroolefines by using $1d_0$ as bifunctional organocatalyst: To the precooled (-10°C) cyclohexanone (2.6 ml, 25 mmol) the catalyst $1d_0$ (5.35 mg, 10 mol%) was added under nitrogen atmosphere. The reaction allowed to stir for about 1h and then trans-nitrostyrene (1 mmol) and degassed triethyl amine (0.028 ml, 20 mol%) were added by maintaining the nitrogen atmosphere. The reaction was evaporated under reduced pressure after completion. To the reaction crude water was added and then extracted with EtOAc (10 ml X 3) and combined organic layer dried over Na_2SO_4 and evaporated by rotatory evaporator. The Michael products was purified by column chromatography using15-20% EtOAc and hexane as eluent.

General reaction condition for the Michael addition of Michael donors to Nitroolefines by using $1d_0$ as bifunctional organocatalysts: To the precooled (-10°C) **10** (20 mmol) the catalyst $1d_0$ (5.35 mg, 10 mol%) was added under nitrogen atmosphere. The reaction allowed to stir for about 1h and then trans-nitrostyrene (1 mmol) was added by maintaining the nitrogen atmosphere. The reaction was evaporated under reduced pressure after completion. To the reaction crude water was added and then extracted with EtOAc (10 ml X3) and combined organic layer dried over Na_2SO_4 and evaporated by rotatory evaporator. The products were purified by column chromatography using 20% EtOAc and hexane as eluent.

The enantiomeric excess was determined by the HPLC analysis in which series 5 and 11 compounds were further purified by flash chromatography after obtaining the NMR and other data.

Acknowledgements

CSA acknowledge Guru Gobind Singh Indraprastha Univeristy, New Delhi for the financial assistance and TRC lab for providing analytical data. IAK is thankful to UGC for granting Dr. D.S. Kothari postdoctoral fellowship.

Notes and references

1 (a) X. Fang and C.-J. Wang, *Chem. Commun.*, 2015, **51**, 1185-1197; (b) Y. Kobayashi and Y. Takemoto, Bifunctional Guanidines as Hydrogen-Bond-Donating Catalysts. Chapter, Part of the series *Topics in Heterocyclic Chemistry* pp 1-24 , Springer Berlin Heidelberg, Berlin, Heidelberg 2015, DOI: 10.1007/7081_2015_155; (c) Y. Takemoto, *Chem. Pharma. Bull.*, 2010, **58**, 593; (d) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672-12673; (e) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119-125.

2 (a) C. Rabalakos and W. D. Wulff, *J. Am. Chem. Soc.*, 2008, **130**, 13524-13525; (b) J. Wang, H. Li, W. Duan, L. Zu and W. Wang, *Org. Lett.*, 2005, **7**, 4713-4716; (c) J. Song, Y. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 6048-6049; (d) K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2011, **133**, 16711-16713; (e) S. H. McCooey and S. J. Connon, *Angew. Chem. Int. Edit.*, 2005, **117**, 6525-6528; (f) H. Y. Bae and C. E. Song, *ACS Catalysis*, 2015, **5**, 3613-3619; (g) J. M. Andres, R. Manzano and R. Pedrosa, *Chem.-Eur. J.*, 2008, **14**, 5116-5119.

3 A. M. Faisca Phillips, *Eur. J. Org. Chem.*, 2014, **2014**, 7291-7303.

4 C. Becker, C. Hoben and H. Kunz, *Adv. Synth. Catal.*, 2007, **349**, 417-424.

5 K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li and J.-A. Ma, *Org. Lett.*, 2007, **9**, 923-925.

6 (a) H. N. Yuan, S. Wang, J. Nie, W. Meng, Q. Yao and J. A. Ma, *Angew. Chem. Int. Edit.*, 2013, **52**, 3869-3873; (b) A. Lu, K. Hu, Y. Wang, H. Song, Z. Zhou, J. Fang and C. Tang, *J. Org. Chem.*, 2012, **77**, 6208-6214; (c) S. Kong, W. Fan, G. Wu and Z. Miao, *Angew. Chem. Int. Edit.*, 2012, **51**, 8864-8867; (d) H. Ma, K. Liu, F.-G. Zhang, C.-L. Zhu, J. Nie and J.-A. Ma, *J. Org. Chem.*, 2010, **75**, 1402-1409; (e) X. Pu, P. Li, F. Peng, X. Li, H. Zhang and Z. Shao, *Eur. J. Org. Chem.*, 2009, **2009**, 4622-4626; (f) Y. Wang, H. Yang, J. Yu, Z. Miao and R. Chen, *Adv. Synth. Catal.*, 2009, **351**, 3057-3062; (g) A. Lu, P. Gao, Y. Wu, Y. Wang, Z. Zhou and C. Tang, *Org. Biomol. Chem.*, 2009, 7, 3141-3147; (h) A. Puglisi, M.

View Article Online
DOI: 10.1039/C6OB02158A

Benaglia, L. Raimondi, L. Lay and L. Poletti, *Org. Biomol. Chem.*, 2011, **9**, 3295-3302; (i) P. Gao, C. Wang, Y. Wu, Z. Zhou and C. Tang, *Eur. J. Org. Chem.*, 2008, **2008**, 4563-4566.

7 (a) K. Ágoston and P. Fügedi, *Carbohyd. Res.*, 2014, **389**, 50-56; (b) M. Turks, E. Rolava, D. Stepanovs, A. Mishnev and D. Marković, *Tetrahedron: Asymmetry*, 2015, **26**, 952-960.

8 (a) C. S. Azad and A. K. Saxena, *Org. Chem. Front.*, 2015, **2**, 665-669; (b) C. S. Azad and A. K. Saxena, *Tetrahedron*, 2013, **69**, 2608-2612; (c) C. S. Azad, S. S. Bhunia, A. Krishna, P. K. Shukla and A. K. Saxena, *Chem. Bio. Drug Des.*, 2015, **86**, 440-446.

9 (a) C.-L. Cao, M.-C. Ye, X.-L. Sun and Y. Tang, *Org. Lett.*, 2006, **8**, 2901-2904; (b) Y. Takemoto, *J. Syn. Org. Chem. Japan*, 2006, **64**, 1139-1147.

10 (a) K. Miyamoto, Y. Sakai, S. Goda and M. Ochiai, *Chem. Commun.*, 2012, **48**, 982-984; (b) C. Yu, Y. Jiang, B. Liu and L. Hu, *Tetrahedron Lett.*, 2001, **42**, 1449-1452; (c) T. K. Chakraborty and A. Ghosh, *Tetrahedron Lett.*, 2002, **43**, 9691-9693.

11 (a) M. Işık, M. Y. Unver and C. Tanyeli, *J. Org. Chem.*, 2015, **80**, 828-835; (b) U. Vural, M. Durmaz and A. Sirit, *Org. Chem. Front.*, 2016; DOI: 10.1039/C6QO00135A; (c) H. Y. Bae and C. E. Song, *ACS Catalysis*, 2015, **5**, 3613-3619; (d) B. List, P. Pojarliev and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423-2425; (e) J. M. Betancort, K. Sakthivel, R. Thayumanavan and C. F. Barbas, *Tetrahedron Lett.*, 2001, **42**, 4441-4444.

12 (a) G. Calderari and D. Seebach, *Helv. Chim. Acta*, 1995, **58**, 1592−1604; (b) M. P. Sibi and S. Manyem, *Tetrahedron*, 2000, **56**, 8033-8061; (c) N. Ono, The Nitro Group in Organic Synthesis; Wiley-VCH: New York, 2001; (d) J. Christoffers and A. Baro, *Angew. Chem. Int. Edit.*, 2003, **42**, 1688-1690; (e) C. Czekelius and E. M. Carreira, *Angew. Chem. Int. Edit.*, 2005, **44**, 612-615; (f) S. Patterson and S. Wyllie, *Trends Parasitolo.*, 2014, **30**, 289-298; (g) C. S. Azad, V. M. Balaramnavar, I. A. Khan, P. K. Doharey, J. K. Saxena and A. K. Saxena, *RSC Adv.*, 2015, **5**, 82208-82214; (h) C. S. Azad and A. K. Narula, *RSC Adv.*, 2016, **6**, 19052-19059.

13 P. J. Chua, B. Tan, X. Zeng and G. Zhong, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3915-3918; (b) K. Hu, T. Liu, A. Lu, Y. Liu, Y. Wang, G. Wu, Z. Zhou and C. Tang, *Eur. J. Org. Chem.*, 2011, **2011**, 3507-3513; (c) D.-Q. Xu, H.-D. Yue, S.-P. Luo, A.-B. Xia, S. Zhang and Z.-Y. Xu, *Org. Biomol. Chem.*, 2008, **6**, 2054-2057; (d) X.-j. Zhang, S.-p. Liu, X.-m. Li, M. Yan and A. S. Chan, *Chem. Commun.*, 2009, 833-835; (e) J. Liu, Z. Yang, X. Liu, Z. Wang, Y. Liu, S. Bai, L. Lin and X. Feng, *Org. Biomol. Chem.*, 2009, **7**, 4120-4127; (f) J.-R. Chen, Y.-J. Cao, Y.-Q. Zou, F. Tan, L. Fu, X.-Y. Zhu and W.-J. Xiao, *Org. Biomol. Chem.*, 2010, **8**, 1275-1279; (g) X.-Q. Dong, H.-L. Teng, M.-C. Tong, H. Huang, H.-Y. Tao and C.-J. Wang, *Chem. Commun.*, 2010, **46**, 6840-6842.

14 (a) H. Jin, S. T. Kim, G.-S. Hwang and D. H. Ryu, *J. Org. Chem.*, 2016, **81**, 3263-3274; (b) T. Sekikawa, T. Kitaguchi, H. Kitaura, T. Minami and Y. Hatanaka, *Org. Lett.*, 2015, **17**, 3026-3029; (c) C.-J. Wang, Z.-H. Zhang, X.-Q. Dong and X.-J. Wu, *Chem. Commun.*, 2008, 1431-1433.

15 (a) P. S. Hynes, P. A. Stupple and D. J. Dixon, *Org. Lett.*, 2008, **10**, 1389-1391; (b) T. Tsubogo, H. Oyamada and S. Kobayashi, *Nature*, 2015, **520**, 329-332.

16 (a) D. Wei, L. Fang, M. Tang and C.-G. Zhan, *J. Phys. Chem. B*, 2013, **117**, 13418-13434; (b) R. Lee, F. Zhong, B. Zheng, Y. Meng, Y. Lu and K.-W. Huang, *Org. Biomol. Chem.*, 2013, **11**, 4818-4824; (c) M. M. Vallejos, N. M. Peruchena and S. C. Pellegrinet, *Org. Biomol. Chem.*, 2013, **11**, 7953-7965; (d) D. Wei, X. Huang, J. Liu, M. Tang and C.-G. Zhan, *Biochemistry*, 2013, **52**, 5145-5154; (e) D. Wei, B. Lei, M. Tang and C.-G. Zhan, *J. Am. Chem. Soc.*, 2012, **134**, 10436-10450; (f) W. Zhang, Y. Zhu, D. Wei and M. Tang, *J. Comput. Chem.*, 2012, **33**, 715-722; (g) D. Wei and M. Tang, *J. Phys. Chem. A*, 2009, **113**, 11035-11041; (h) E. H. Krenske, *Org. Biomol. Chem.*, 2013, **11**, 5226-5232.

17 Desmond Molecular Dynamics System, D. E. Shaw Research, New York, NY, 2016. Maestro-Desmond Interoperability Tools, Schrödinger, New York, NY, 2016.

18 The orientation of the phenyl part of NS with aryl half of the catalyst and enolate formation at C2` and C6` of cyclohexanone may results to the formation of the all the possible stereoisomers. Thus the formation of SR and SS product was studied due the reason that RS and RR configuration could be able to achieve when the orientation of the phenyl NS and aryl half of the catalyst are away from each other, whereas the orientation of phenyl part of NS was considered towards the aryl half of the catalyst due difference of 25.7kcal/mol energy.