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Studies on the influence of saccharide fragment of urea organocatalysts on the yield and enantioselectivity of aza-Henry reaction

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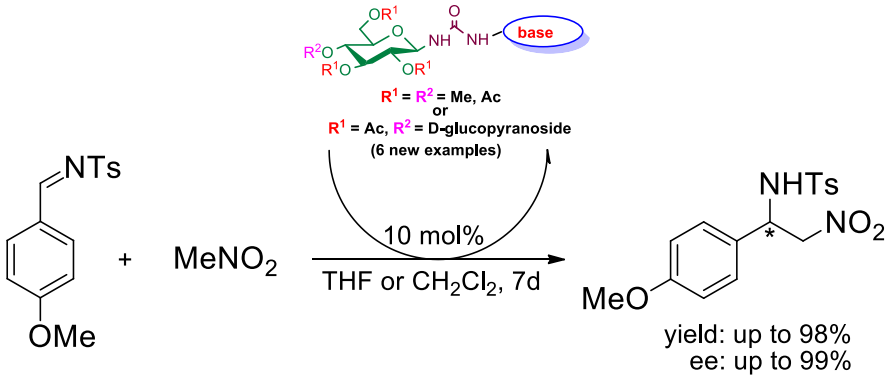
Abstract

Six new bifunctional ureas bearing a carbohydrate ring and an optically active base for the asymmetric aza-Henry reaction of imines with nitromethane has been developed. The influence of the saccharide urea fragment and the base in organocatalysts, both new and previously prepared by our team, on the yield and enantioselectivity of aza-Henry reactions was demonstrated. The aza-Henry reaction products were obtained in 17-98% yield and ee up to 99%. The highly enantioselective reaction course is likely the result of the synergic action of two urea fragments - saccharide and DACH.



Keywords: aza-Henry reaction, saccharides, urea, organocatalyst

Introduction

Over the past decade, a number of enantioselective transformations of organic compounds promoted by metal-free organocatalysts have been described in the literature. We are still observinge an increase in research on organocatalysts, including sugar derivatives. On the whole, carbohydrate derivatives possess certain distinct advantages. They are inexpensive and readily available natural materials employed as chiral backbones of organocatalysts.[1-21]

An example of such a stereocontrolled synthesis catalyzed by sugar derivatives is the aza-Henry reaction, which involves the nucleophilic addition of nitroalkanes to imines, and results in the formation of a new carbon-carbon bond, and, consequently, a *β*-nitroamine. The resulting *β*-nitroamines represent interesting and useful synthetic building blocks in organic synthesis. What is particularly interesting is the reduction of the nitro group to an amine, leading to the corresponding 1,2-diamines, of great value in both synthesis and biology.[22-28]

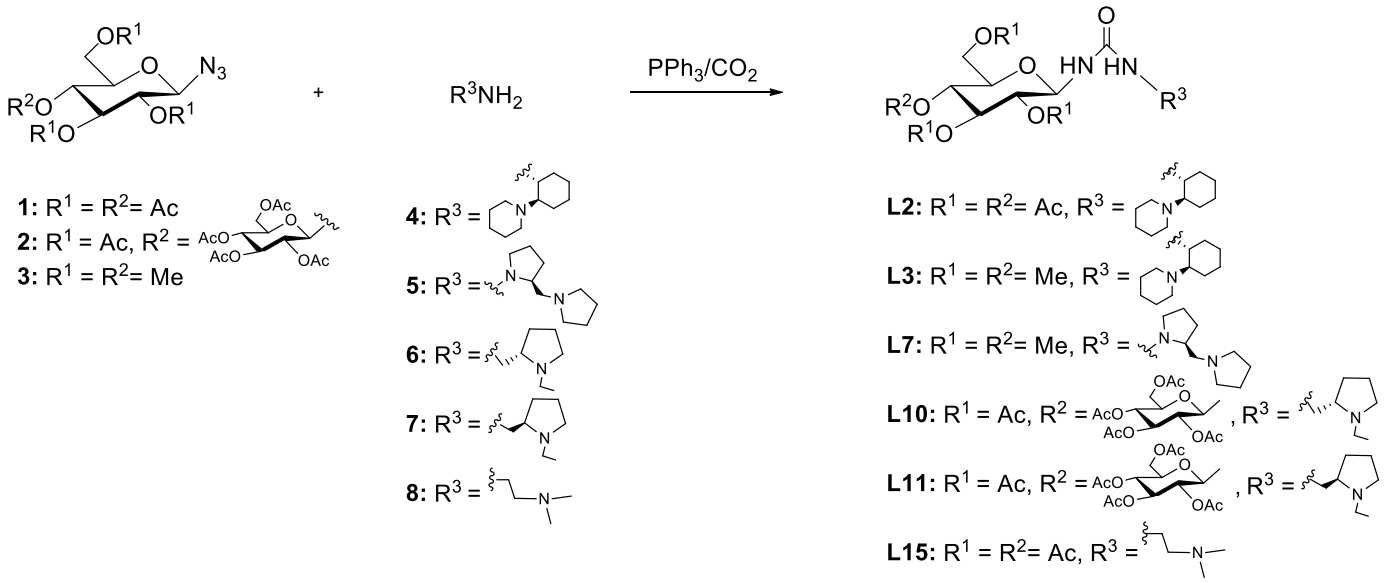
This publication summarizes our research on the effect of the saccharide fragment of organocatalysts on enantioselectivity and yield of the aza-Henry reaction. For this purpose, we prepared an additional six new organocatalysts containing different fragments of sugars, and, subsequently, studied their effectiveness in the reaction of the corresponding imine with nitromethane.

Results and Discussion

Synthesis of organocatalysts L1-L15

The selected urea organocatalysts containing the saccharide ring are summarized in Figure 1. Catalysts **L4**-**L6**, **L8**-**L9,** and **L12**-**L14** were previously synthesized in our group,[29-31] while the derivatives **L1**-**L3**, **L7**, **L10**-**L11,** and **L15** are new compounds, not yet described in the chemical literature.

The simple synthetic route leading to a series of new organocatalysts is shown in Scheme 1.



Scheme 1. Synthesis of new urea organocatalysts.

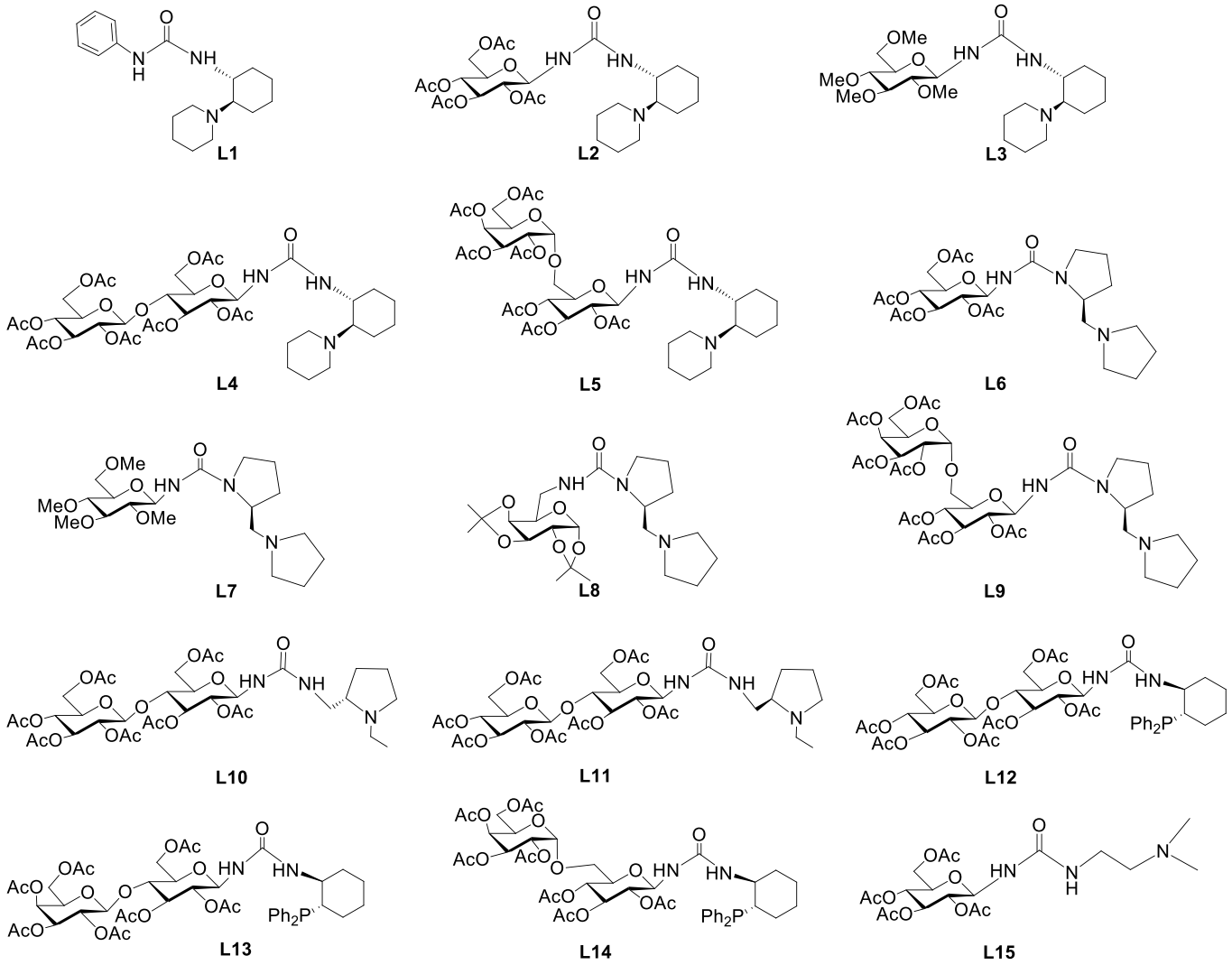
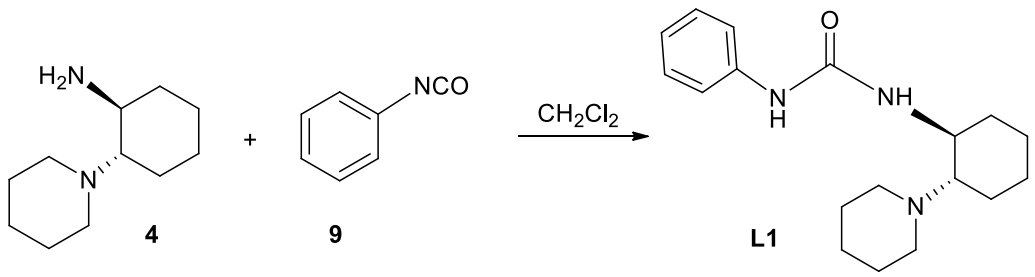


Figure 1. Organocatalysts screening.

The new carbohydrate ureas **L2**-**L3**, **L7**, **L10**-**L11,** and **L15** were synthesized according to the previously described method[29-31] from cellobiose azide **2**[33]or glucose azides **1**[34], **3**[35] and amines **4-8** using CO_2 in the presence of triphenylphosphine in anhydrous toluene. After the usual workup procedure and chromatographic purification, derivatives **L2-L7** were obtained in 68-97% yields. Analytical and spectroscopic data of the compounds are perfectly consistent with the proposed structures. In turn, chiral organocatalyst **L1** was easily synthesized by condensation of cyclohexanediamine **4** with phenyl isocyanate **9** in dichloromethane at room temperature (Scheme 2).

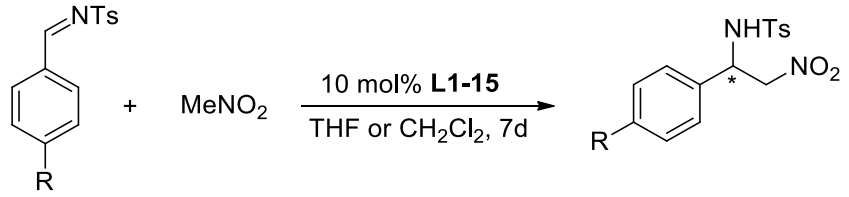


Scheme 2. Synthesis of urea organocatalyst **L1**.

Asymmetric aza-Henry reaction catalyzed by carbohydrate ureas L1-L15

In two of our publications, the discussions on the reactivity and selectivity of various carbohydrate ureas were described.[29-32] Continuing this study, we demonstrate the results obtained in the presence of new ligands in the asymmetric aza-Henry reaction (Table 1). The previously obtained results are also included in Table 1, in order to demonstrate the influence of the sugar moiety and the base on the reactivity and selectivity of this reaction.

Table 1. The asymmetric aza-Henry reaction catalyzed by carbohydrate ureas **L1**-**L15**



Entry	R	Catalyst	Solvent	Yield[a] (%)	ee[b](%)(*S*)	Ref.
1	OMe	**L1**	THF	36	14	
2	OMe	**L1**	CH_2Cl_2	65	32	
3	OMe	**L2**	THF	41	78	
4	OMe	**L2**	CH_2Cl_2	59	99	
5	OMe	**L3**	THF	18	1	
6	OMe	**L3**	CH_2Cl_2	47	37	
7	OMe	**L4**	THF	95	37	[30]
8	OMe	**L4**	CH_2Cl_2	88	16	[30]
9	OMe	**L5**	THF	98	99	[30]
10	OMe	**L5**	CH_2Cl_2	98	97	[30]
11	OMe	**L6**	THF	59	72	[30]
12	OMe	**L6**	CH_2Cl_2	35	70	[30]
13	OMe	**L7**	THF	53	11	
14	OMe	**L7**	CH_2Cl_2	76	49	
15	OMe	**L8**	THF	82	75	[30]
16	OMe	**L8**	CH_2Cl_2	35	67	[30]
17	OMe	**L9**	THF	53	64	[30]
18	OMe	**L10**	THF	47	25	
19	OMe	**L10**	CH_2Cl_2	30	36	
20	OMe	**L11**	THF	58	94	
21	OMe	**L11**	CH_2Cl_2	47	50	
22	H	**L12**	THF	70	0	[29,31]
23	OMe	**L12**	THF	0	-	
24	H	**L13**	THF	45	4	[29]
25	H	**L14**	THF	90	2	[29]
26	OMe	**L15**	CH_2Cl_2	78	8	

[a] Yield refers to isolated products after column chromatography.

[b] Enantioselectivity was measured by HPLC on a Chiralpak OD-H column (25 cm x 4.6 mm); flow rate = 1.0 mL min^{-1}; hexane/*i*-propanol (85/15), detection 215 nm, t_R (*S*) = 34.0 min and t_R (*R*) = 38.3 min.[37]

The asymmetric aza-Henry reaction of *N*-tosyl imine with nitromethane, as the model transformation was carried out under standard conditions - in THF or dichloromethane at room temperature.

Initially, we performed a reaction of methoxy-benzylidene sulfonamide with nitromethane in the presence of urea organocatalyst **L1**, which did not have a chiral sugar fragment. Such a structure of the organocatalyst will allow us to demonstrate the effect of the sugar moiety or its absence on the yield and enantioselectivity of the tested reaction.

The use of organocatalyst **L1** produced 36% and 65% yields of the product in THF and CH_2Cl_2, respectively. The obtained enantioselectivity was 14% and 32% ee in favor of the (*S*)-enantiomer (Table 1, entries 1-2). Subsequently, we analyzed the influence of the sugar moiety of ureas containing the same fragment of diaminocyclohexane derivative (Table 1, entries 3-10). Under identical conditions of aza-Henry reaction, two differently protected glucose derivatives **L2** with acetyl and **L3** with methyl were not particularly active and gave rise to a final product with low yields, though enantioselectivity for the derivative **L2** was satisfactory – ee up to 99% (Table 2, entries 3-6). A significant increase in yield was observed when the cellobiose derivative **L4** was used as a catalyst (Table 1, entries 9-10). In turn, the use of the **L5** organocatalyst, both in THF and CH_2Cl_2, led to a product in excellent yield (98%) and enantioselectivity (99% ee). Such a course of the reaction is likely the result of the synergic action of two urea fragments (saccharide and DACH) of the **L5** derivative (Table 1, entries 9-10).

Another group of urea organocatalysts, the activity of which we examined in the aza-Henry reaction, were mono- and disaccharide derivatives containing the proline ring as a second scaffold (Table 1, entries 11-21). In the series of the monosaccharide catalysts **L6**-**L8**, the best of the sugar has proven to be glucose derivative **L8**, with the isopropyl protecting groups: 82% yield and 75% ee in THF (Table 1, entries 15-16). In contrast, the melibiose derivative **L9** proved to be less active and resulted in a reaction product in 53% yield and 64% ee. The use of both diastereomeric ligands of proline **L10** and **L11** led to the formation of chiral amines with the same absolute configuration. Thus, the stereogenic centers located in the proline moieties do not exert a decisive effect on the absolute configuration of the products (Table 1, entries 18-21).

Finally, we decided to investigate the catalytic activity of **L12**-**L15** derivatives. The replacement of the tertiary amine with a diphenylphosphine substituent (weaker base) in the cyclohexane ureas **L12**, **L13**, and **L14**, or the use of an optically inactive (dimethylamino)ethyl group, as in **L15**, resulted in a drastic decrease in the enantioselectivity of the reaction (Table 1, entries 22-26). Furthermore, urea **L12**, derived from (1*S*,2*S*)-2-(diphenylphosphino)cyclohexane bearing a cellobiosyl scaffold, failed to demonstrate any catalytic activity on the imine with an electron-donating group (Table 1, entry 23).

Conclusions

We presented the synthesis of new urea organocatalysts containing, in addition to an optically active base, a carbohydrate ring as a component of a natural chiral pool. The obtained sugar derivatives proved to be useful and highly effective catalysts for the enantioselective aza-Henry reaction. The best results were obtained for the urea organocatalyst containing structure of melibiose and *trans*-2-(1-piperidinyl)cyclohexylamine fragments. The highly enantioselective reaction course (ee up to 99%) is likely the result of the synergic action of two urea fragments - saccharide and DACH.

Experimental Section

General. All solvents and reagents (amines **4-6**, nitromethane, and imine) were purchased from Sigma-Aldrich and used as supplied, without additional purification. NMR spectra were recorded in $CDCl_3$, on a Bruker Avance III (600 MHz for ^{1}H NMR, 150 MHz for ^{13}C NMR), and coupling constants are reported in Hz. The optical rotation was measured on a Perkin-Elmer 241 MC polarimeter with a sodium lamp at room temperature. The melting points were determined on a DigiMelt apparatus and remain uncorrected. Chromatographic purification of the compounds was achieved with 230-400 mesh size silica gel. The progress of the reactions was monitored by silica gel thin-layer chromatography plates (Merck TLC Silica gel 60 F_{254}). The IR spectra were recorded on a FT-IR Nexus spectrometer. The enantiomeric ratio was determined by using a HPLC (ProStar Varian) employing a Chiralpak OD-H column (25 cm x 4.6 mm).

General procedure for the synthesis of catalysts L2-7

Triphenylphosphine (865 mg, 3.3 mmol) was added to a solution of azidosaccharide (1.1 mmol) in toluene (8 mL). The resulting solution was stirred at room temperature for 1 h and then flushed with CO_2. Next, the appropriate amine (1 mmol) was added. The mixture was stirred for 24 h under CO_2 bubbling conditions. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel eluting with ethyl EtOAc/Hexane or EtOAc/MeOH.

***N*-[(1*R*,2*R*)-*trans*-2-(1-Piperidinyl)cyclohex-1-yl]-*N'*-phenylurea (L1).** Yellow solid (256 mg, 85%); R_f = 0.62 (AcOEt/MeOH, 7:3); mp 91-92˚C; $[\alpha]_D^{20}$ = -43.2 (c 0.5, CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3316, 3073, 2931, 2885, 1729, 1654, 1273, 774, 693. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.07-1.15 (m, 1H, H-6b), 1.15-1.27 (m, 2H, H-3b, H-4b), 1.27-1.37 (m, 1H, H-5b), 1.39-1.45 (m, 2H, 2H-4'), 1.45-1. 54 (m, 2H H-3'b H-5'b), 1.54-1.63 (m, 2H, H-3'a, H-5'a), 1.65-1.71 (m, 1H, H-5a), 1.78-1.84 (m, 1H, H-3a), 1.85-1.92 (m, 1H, H-4a), 2.26 -2.39 (m, 3H, H-2, H-2'b, H-6'b), 2.51-2.57 (m, 1H, H-6a), 2.62 -2.71 (m, 2H, H-2'a, H-6'a), 3.43-3.48 (m, 1H, H-1), 7.03-7.08 (m, 1H, NH), 7.25-7.34 (m, 6H, Ar, 1NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 23.1 (C-4), 24.4 (C-5), 24.5 (C-4'), 25.6 (C-3), 26.1 (C3', C5'), 33.6 (C-6), 49.1 (C-2', C-6'), 50.8 (C-1), 67.9 (C-2), 120.8-129.1 (C-Ar), 156.4 (CO, Urea). Anal. calcd. for $C_{18}H_{27}N_3O$ (301.42): C, 71.72; H, 9.03; N, 13.94%. Found: C, 71.44; H, 9.31; N, 14.02%.

***N*-[(1*R*,2*R*)-*trans*-2-(1-Piperidinyl)cyclohexylamine]-*N'*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl)urea (L2).** White powder (538 mg, 97%); R_f = 0.80 (AcOEt/MeOH, 4:1); mp 103-106˚C; $[\alpha]_D^{25}$ = -30.4 (c 0.5, CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3378, 2934, 1756, 1659, 1231, 1037. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 0.97-1.07 (m, 1H, H-6'b), 1.13-1.22 (m, 2H, H-3'b, H-4'b), 1.22-1.33 (m, 1H, H-5''b), 1.36-1.46 (m, 2H, 2H-4''), 1.46-1.60 (m, 4H, 2H-3'', 2H-5''), 1.60-1.68 (m, 1H, H-5'a), 1.74-1.81 (m, 1H, H-4'a), 1.81-1.89 (m, 1H, H-3'a), 2.01- 2.07 (4s, 12H, 4CH_3, Ac),2.14-2.21 (m, 1H, H-2'), 2.22-2.33 (m, 2H, H-2''b, H-6"b), 2.45-2.51 (m, 1H, H-6'a), 2.53-2.62 (m, 2H, H-2''a, H-6''a), 3.26-3,34 (m, 1H, H-1'), 3.79 (ddd, 1H, H-5, $J_{5,4}$ 9.6, $J_{5,6a}$ 4.2, $J_{5,6b}$ 2.2), 4.08 (dd, 1H, H-6b, $J_{6b,6a}$ 12.0, $J_{6b,5}$ 2.2), 4.92 (t, 1H, H-2, $J_{2,3}$ 9.6, $J_{2,1}$ 9.3), 5.07 (t, 1H, H-4, $J_{4,3}$ 9.6, $J_{4,5}$ 9.6), 5.08-5.14 (m, 1H, NH), 5.17(t, 1H, H-1, $J_{1,NH}$ 9.3, $J_{1,2}$ 9.3), 5.30 (t, 1H, H-3, $J_{3,2}$ 9.6, $J_{3,4}$ 9.6), 5.58-5.42 (m, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 20.6-20.7 (4CH_3, Ac), 22.9 (C-3'), 24.5 (C-5'), 24.8 (C-4''), 25.6 (C-4'), 26.5 (C-5'', C3''), 33.3 (C-6'), 49.2 (C-2''), 51.2 (C-1'), 61.9 (C-6), 67.9 (C-2'), 68.5 (C-4), 70.8 (C-2), 73.1 (C-3), 73.2 (C-5), 80.4 (C-1), 156.8 (CO, Urea), 171.1-169.6 (4CO, Ac). Anal. calcd. for $C_{28}H_{41}N_3O_{10}$ (555.62): C, 56.20; H, 7.44; N, 7.56%. Found: C, 56.35; H, 7.72; N, 7.42%.

***N*-[(1*R*,2*R*)-*trans*-2-(1-Piperidinyl)cyclohex-1-yl]-*N'*-(2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosyl)urea (L3).** White powder (319 mg, 72%); R_f = 0.71 (AcOEt/MeOH, 7:3); mp 182-183˚C; $[\alpha]_D^{22}$ = -5.6 (c 0.5, CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3424, 3330, 2931, 1647, 1565, 1111. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 0.99-1.09 (m, 1H, H-6'b), 1.12-1.22 (m, 2H, H-3'b, H-4'b), 1.23-1.32 (m, 1H, H-5'b), 1.34-1.44 (m, 2H, 2H-4''), 1.44-1.59 (m, 4H, 2H-3'', 2H-5''), 1.60-1.67 (m, 1H, H-5'a), 1.74-1.80 (m, 1H, H-3'a), 1.81-1.88 (m, 1H, H-4'a), 2.140-2.21 (m, 1H, H-2'), 2.23-2.31

(m, 2H, H-2', H-6''b), 2.52-2.63 (m, 3H, H-6'a, H-2''a, H-6''a), 2.96 (t, 1H, H-2, $J_{2,3}$ 8.7, $J_{2,1}$ 8.8), 3,23 (t, 1H, H-4, $J_{4,3}$ 8.7, $J_{4,5}$ 9.0), 3.25 (t, H, H-3, $J_{3,2}$ 8.7, $J_{3,4}$ 8.7), 3.34 (ddd, 1H, H-5, $J_{5,4}$ 9.0, $J_{5,6a}$ 1.9, $J_{5,6b}$ 3.6), 3.32-3.37 (m, 1H, H-1'), 3.38 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 3.54 (dd, 1H, H-6b, $J_{6b,6a}$ 10.5, $J_{6b,5}$ 3.6), 3.62 (dd, 1H, H-6a, $J_{6a,5}$=1.9, $J_{6a,6b}$=10.5), 3.64 (s, 3H, CH_3), 4.75 (t, 1H, H-1, $J_{1,2}$ 8.8, $J_{1,NH}$ 8.0), 4.80(d, 1H, NH, $J_{NH,1}$ 8.0), 5.68 (sl, 1H, NH); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 23.03 (C-4'), 24.57 (C-5'), 24.83 (C-4''), 25.75 (C-3'), 26.66 (C-3'', C-5''), 33.33 (C-6'), 49.32 (C-2'', C-6''), 68.11 C-2', 59.11, 59.83, 60.11, 60.11 ($4CH_3$), 70.91 (C-6), 75.98 (C-5), 79.46 (C-4), 81.77 (C-1), 82.89 (C-2), 87.22 (C-3), 157.70 (CO, Urea). Anal. calcd. for $C_{22}H_{41}N_3O_6$ (443.30): C, 59.57; H, 9.32; N, 9.47%. Found: C, 59.32; H, 9.04; N, 9.28%.

***N*-[(1*R*, 2*R*)-*trans*-2-(1-Piperidinyl)cyclohexylamine]-*N'*-(2,3,6 ,2',3',4',6'-hepta-*O*-acethyl-β-D-cellobiosyl)-urea (L4).** Synthesis and spectral data for **L4** see Ref. 30

***N*-[(1*R*, 2*R*)-*trans*-2-(1-Piperidinyl)cyclohexylamine]-*N'* - (2,3,6,2',3',4',6'-hepta-*O*-acethyl-β-D-melibiosyl)-urea (L5).** Synthesis and spectral data for **L5** see Ref. 30

***N*-[(*S*)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine]-*N'*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (L6).** synthesis and spectral data for **L6** see Ref. 30

***N*-[(S)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine]-*N*'-(2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosyl)urea (L7).** colourless oil **(**281 mg, 68%); R_f = 0.71 (AcOEt/MeOH, 7:3); $[\alpha]_D^{22}$= - 6.0 (c 0.5, CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3477, 33382, 2956, 1632, 1547, 1109. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.54-1.65 (m, 1H, H-3'), 1.69-1.87 (m, 6H, 2H-3'', 2H-4'', 2H-4'), 2.00-2.09 (m, 1H, H3'a), 2.44 (dd, 1H, H6''b, $J_{6''a,6''b}$ 13.5, $J_{6''b,\,2'}$ 1.6), 2.54-2.61 (m, 2H, H-2''b, H-5''b), 2.65-2.73 (m, 2H, H-2''a, H-5''a), 2.80 (t, 1H, H-2, $J_{2,1}$ 9.3, $J_{2,3}$ 9.4), 2.82 (dl, 1H, H''a, $J_{6''a,6''b}$ 13.5, $J_{6''a,2'}$ 1.0), 3.11 (t, 1H, H-4, $J_{4,3}$ 9.0, $J_{4,5}$ 9.0), 3.19 (t, 1H, H-3, $J_{3,2}$ 9.4, $J_{3,4}$ 9.0), 3.26-3.36 (m, 2H, H-5, H-5'b), 3.29 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 3.55-3.57 (m, 2H, H-6a, H-6b), 3.60 (s, 3H, CH_3), 3.68-3.76 (m, 1H, H-5'a), 3.75-3.84 (m, 1H, H-2'), 4.88 (t, 1H, H-1, $J_{1,2}$ 9.3, $J_{1,NH}$ 9.4); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 23.5, 23.7 (C-4', C-3'', C4''), 32.3 (C-3'), 47.1 (C-5'), 54.4 (C-2'', C-5''), 57.1 (C2'), 63.3 (C-6"), 59.1, 59.8, 60.1, 60.7 ($4CH_3$), 71.2 (C-6), 75.9 (C-5), 79.7 (C-4), 81.1 (C-1), 83.8 (C-2), 87.2 (C-3), 158.36 (CO, Urea). Anal. calcd. for $C_{20}H_{37}N_3O_6$ (415.27): C, 57.81; H, 8.89; N, 10.11%. Found: C, 57.40; H, 9.07; N, 9.87%.

***N*-[(*S*)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine]-*N'*-(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose)]urea (L8).** Synthesis and spectral data for **L8** see Ref. 30

***N*-[(*S*)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine]-*N'*-(2,3,6,2',3',4',6'-hepta-*O*-acethyl-β-D-melibiosyl)-urea (L9).** Synthesis and spectral data for **L9** see Ref. 30

***N*-[(2*S*)-1-Ethyl-pyrrolidin-2ylmethyl]-*N'*-(2,3,6,2',3',4'6'-hepta-*O*-acetyl-β-D-cellobiosyl)urea (L10):** White powder (552 mg, 75%); R_f = 0.78 (AcOEt/MeOH, 7:3); mp 160-161˚C; $[\alpha]_D^{22}$ = -7.2(c 0.5, CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3405, 1751, 1688, 1232, 1042. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.09 (t, 3H, H-8'', $J_{8'',7''}$ 7.2), 1.49-1.57 (m, 1H, H-3''b), 1.59-1.74 (m, 2H, H-4''a, H-4''b), 1.78-1.84 (m, 1H, H-3''a), 1.85-1.93 (m, 1H, H-5''b), 1.98-2.10 (7s, CH_3, Ac), 2.12-2.19 (m, 1H, H-6''b), 2.20-2.27 (m, 1H, H-7''b), 2.51-2.60 (m, 1H, H-2''), 2.75-2.28 (m, 1H, H-7''a), 3.05-3.10 (m, 1H, H-6''a), 3.11-3.17 (m, 1H, H-5''a), 3.17-3.34 (m, 1H, NH), 3.65 (ddd, 1H, H-5', $J_{5',6'a}$ 2.0, $J_{5',6'b}$ 2.0, $J_{5',4'}$ 9.5), 3.70 (ddd, 1H, H-5, $J_{5,6a}$ 1.1, $J_{5,6b}$ 4.5, $J_{5,4}$ 9.5), 3.77 (t, 1H, H-4, $J_{3,4}$ 9.4, $J_{4,5}$ 9.5), 4.05 (dd, 1H, H-6'b, $J_{5',6'b}$= 2.0, $J_{6'a,6'b}$ =12.4), 4.13 (dd, 1H, H-6b, $J_{5,6b}$=4.5, $J_{6a,6b}$=12.0), 4.37 (dd, 1H, H-6'a, $J_{5,6'a}$ 2.0, $J_{6'a,6'b}$ 12.4), 4.46 (dd, 1H, H-6a, $J_{6a,6b}$ 12.0, $J_{6a,5}$ 1.1), 4.51 (d, 1H, H-1', $J_{1',2'}$ 9.1), 4.82 (t, 1H, H-2, $J_{2,1}$ 9.4, $J_{2,3}$ 9.4), 4.91 (t, 1H, H-2', $J_{2',1'}$ 9.1, $J_{2',3'}$ 9.5), 5.07 (t, 1H, H-4', $J_{4',3'}$ 9.5, $J_{4',5'}$ 9.5), 5.10 (d, 1H, NH, $J_{N\text{-}H,1}$ 9.4), 5.11 (t, 1H, H-3', $J_{3',2'}$ 9.5, $J_{3',4'}$ 9.5), 5.14 (t, 1H, H-1, $J_{1,2}$ 9.4, $J_{1,NH}$ 9.4), 5.25 (t, 1H, H-3, $J_{3,2}$ 9.4, $J_{3,4}$ 9.4); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 13.7 (C-8''), 20.5-20.8 ($7CH_3$, Ac), 23.2 (C-4''), 31.7 (C-3''), 48.6 (C-7''), 53.2 (C-5''), 53.3 (C-6''), 61.7 (C-6'), 62.0 (C-6), 63.2 (C-2''), 67.9 (C-4'), 71.1 (C-2), 71.6 (C-2'), 72.0 (C-5'), 72.6 (C-3), 73.0 (C-3'), 74.1 (C-5), 76.3 (C-4), 80.1 (C-1), 100.6 (C-1'), 157.4 (CO, Urea), 170.5-168.9 (7CO, Ac). Anal. calcd. for $C_{34}H_{51}N_3O_{18}$ (798.77): C, 51.71; H, 6.51; N, 5.32%. Found: C, 51.79; H, 6.54; N, 4.85%.

***N*-[(2*R*)-1-Ethyl-pyrrolidin-2ylmethyl]-*N'*-(2,3,6,2',3',4'6'-hepta-*O*-acetyl-β-D-cellobiosyl)urea (L11).** White powder (530 mg, 72%); R_f = 0.6 (AcOEt/MeOH 7:3); mp 124-125˚C; $[\alpha]_D^{22}$ -31.2(c 0.5, CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3409, 1751, 1655, 1232, 1042. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.08 (t, 3H, H-8'', $J_{8'',7''}$ 6.9), 1.55-1.75 (m, 3H, H-3''b, H-4''a, H-4''b), 1.75-1.87 (m, 1H, H-3''a), 2.00-2.03 (m, 1H, H-5''b), 1.96-2.09 (7s, CH_3, Ac), 2.12-2.18 (m, 1H, H-6''b), 2.20-2.29 (m, 1H, H-7''b), 2.51-2.60 (m, 1H, H-2''), 3.02-3.30 (m, 3H, N-H, H-5''a, H-6''a), 3.64 (ddd, 1H, H-5', $J_{5',6'b}$ 2.2, $J_{5',6'a}$ 4.4, $J_{4',5'}$ 09.7), 3.69 (ddd, 1H, H-5, $J_{5,6a}$ 1.6, $J_{5,6b}$ 4.5, $J_{4,5}$ 9.6), 3.74 (t, 1H, H-4, $J_{4,3}$ 9.4, $J_{4,5}$ 9.6), 3.72-3.84 (m, 1H, H-7''a), 4.03 (dd, 1H, H-6'b, $J_{5',6'b}$ 2.2, $J_{6'a,6'b}$ 12.5), 4.13 (dd, 1H, H-6b, $J_{5,6b}$ 4.5, $J_{6a,6b}$ 12.0), 4.35 (dd, 1H, H-6'a, $J_{5',6'a}$ 4.4, $J_{6'a,6'b}$ 12.5), 4.44 (dd, 1H, H-6a, $J_{6a,6b}$ 12.0, $J_{6a,5}$ 1.6), 4.50 (d, 1H, H-1', $J_{1',2'}$ 7.9), 4.79 (t, 1H, H-2, $J_{2,3}$ 9.4, $J_{2,1}$ 9.5), 4.90 (t, 1H, H-2', $J_{2',3'}$ 9.3, $J_{2',1'}$ 7.9), 5.05 (t, 1H, H-4', $J_{4',3'}$ 9.4, $J_{4',5'}$ 9.7), 5.07 (t, 1H, H-1, $J_{1,2}$ 9.5), 5.12 (t, 1H, H-3', $J_{3'2'}$ 9.3, $J_{3',4'}$ 9.4), 5.24 (t, 1H, H-3, $J_{3,4}$ 9.4, $J_{3,2}$ 9.4), 5.27-5.17 (m, 1H, N-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 13.8 (C-8''), 20.5-20.8 (7CH_3, Ac), 23.2 (C-4''), 27.8 (C-3''), 37.1 (C-5''), 48.5 (C-7''), 53.9 (C-6''), 61.7 (C-6'), 62.1 (C-6), 63.2 (C-2''), 68.0 (C-4'), 71.7 (C-2), 71.8 (C-2'), 72.0 (C-5'), 72.8 (C-3), 73.1 (C-3'), 74.2 (C-5), 76.5 (C-4), 80.2 (C-1), 100.6 (C-1'), 158.5 (CO, Urea), 168.9-170.5 (7CO, Ac). Anal. calcd. for $C_{34}H_{51}N_3O_{18}$ (798.77): C, 51.71; H, 6.51; N, 5.32%. Found: C, 51.60; H, 6.56; N, 5.12%.

***N*-[(1*S*.2*S*)-2-(Diphenylphosphino)cyclohexsyl]-*N'*-(2,3,6, 2',3',4',6'-hexa-*O*-acetyl-β-D-cellobiose)urea (L12).** Synthesis and spectral data for **L12** see Ref. 29,31

***N*-[(1*S*.2*S*)-2-(Diphenylphosphino)cyclohexsyl]-*N'*-(2,3,6, 2',3',4',6'-hexa-*O*-acetyl-β-D-lactose)urea.** Synthesis and spectral data for **L13** see Ref. 29

***N*-[(1*S*.2*S*)-2-(Diphenylphosphino)cyclohexsyl]-*N'*-(2,3,4, 2',3',4',6'-hexa-*O*-acetyl-β-D-melibiose)urea (L14).** Synthesis and spectral data for **L14** see Ref. 29

***N*-(2-*N*,*N*-Dimethylamineth-1yl)-*N'*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl)-urea (L15).** White powder (309 mg, 67%). R_f = 0.63 (MeOH/Acetone, 4:1); mp 45-48˚C; $[\alpha]_D^{22}$= - 6.0 (c 0.5, CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3331, 2985, 1683, 1554, 1162. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.94, 1.95, 1.98, 2.00 (4s, 12H, 4CH_3, Ac), 2.21 (s, 6H, 2CH_3), 2.38-2.42 (m, 2H, 2H-2'), 2.69 (s, 1H, NH), 3.15-3.26 (m, 2H, 2H-1'), 3.76 (ddd, 1H, H-5, $J_{5,6b}$ 2.2, $J_{5,6a}$ 4.1, $J_{5,4}$ 9.5), 4.04 (dd, 1H, H-6b, $J_{6b,5}$ 2.2, $J_{6b,6a}$ 12.5), 5.45 (bs, 1H, NH); 4.23 (dd, 1H, H-6a, $J_{6a,5}$ 4.0, $J_{6a,6b}$ 12.5), 4.85 (t, 1H, H-2, $J_{2,1}$ 9.5, $J_{2,3}$ 9.5), 5.00 (t, 1H, H-4, $J_{4,3}$ 9.5, $J_{4.5}$ 9.5), 5.09 (t, 1H, H-1, $J_{1,2}$ 9.5, $J_{1,NH}$ 9.5), 5.23 (t, 1H, H-3, $J_{3,2}$ 9.5, $J_{3,4}$ 9.5). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 20.6, 20.7, 20.8, 21.0 (4CH_3, Ac), 44.9 (CH_3N), 37.6 (C-1'), 58.5 (C-2'), 61.8 (C-6), 68.3 (C-4), 70.6 (C-2), 73.1 (C-5), 73.2 (C-3), 80.1 (C-1), 156.8 (CO, Urea), 169.9-171.1 (CO, Ac). Anal. calcd. for $C_{19}H_{31}N_3O_{10}$ (461.20): C, 49.45; H, 6.77; N, 9.11%. Found: C, 49.31; H, 6.84; N, 9.15.

Typical procedure for an enantioselective aza-Henry reaction

To the solution of the appropriate organocatalyst (0.01 mmol, 20 mol%) and imine (0.05 mmol) in THF or CH_2Cl_2 (1ml), nitromethane (0.25 mmol) was added. The mixture was stirred for 7 days at room temperature and directly purified by column chromatography on silica gel (Hexane/AcOEt 3/1 as eluent) to yield the desired products. The products are known and our spectroscopic data are consistent with the published data.[29,30,38]

2-Nitro-1-phenyl-*N*-tosylethanamine. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.41 (s, 3H, CH_3), 4.68 (dd, 1H, *J* 6.4, 12.2), 4.84 (dd, 1H, *J* 6.4, 12.2), 4.98 (ddd, 1H, *J* 8.2, 6.4, 6.4), 5.29 (d, 1H, NH, *J* 8.2), 7.08-7.10 (m, 2H, Ar), 7.23-7.27 (m, 5H, Ar), 7.65 (d, 2H, Ar, *J* 8.3).

2-Nitro-1-(4-methoxyphenyl)-*N*-tosylethanamine. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.35 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.58 (dd, 1H, *J* 6.2, 13.3), 4.77 (dd, 1H, *J* 6.2, 13.3), 4.84 (ddd, 1H, *J* 6.2, 6.2, 7.2), 5.09 (d, 1H, NH, *J* 7.2), 6.68-6.72 (m, 2H, Ar), 6.93 (dl, 2H, Ar, *J* 8.6), 7.16-7.21 (m, 2H, Ar), 7.69 (dl, 2H, *J* 8.6).

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