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Enantioselective Organocatalysis of Strecker and Mannich Reactions Based on Carbohydrates

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Dedicated to Professor Joachim Thiem on the occasion of his 65th birthday.

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Abstract: Efficient organocatalysts for enantioselective Strecker and Mannich reactions were constructed from glucosamine as a readily accessible chiral scaffold. A variety of aromatic aldimines were subjected to hydrocyanation with good to excellent yield (72–98%) and, in part, high enantioselectivity (69–95% *ee*). Influence of the catalyst architecture on the enantioselectivity obviously arises from restrictions imposed on the conformational flexibility of the monosaccharidic backbone. In the asymmetric Mannich reaction moderate yields (up to 76%) and enantioselectivities (up to 58% *ee*) have been achieved with the described catalyst.

Keywords: carbohydrate scaffolds; enantioselective organic catalysis; glucosamine derivatives; Mannich reaction; Strecker reaction

Introduction

During the past decade, a number of enantioselective transformations of organic compounds promoted by metal-free organocatalysts have been described.[1] Although carbohydrates meet all requirements put on such an organocatalyst, no example of organocatalysis with a carbohydrate was reported so far. Carbohydrates, i.e., monosaccharides, are conformationally stable, multifunctional, cheap and readily available. Besides their high density of chiral information on one molecular unit, they offer a number of functional groups useful for variation and optimization of the catalysts performance, e.g., by introducing additional stereodifferentiating groups or for immobilization on a polymer support.

We herein report the synthesis of an efficient organocatalyst based on a carbohydrate. It was obtained by structural modifications of D-glucosamine and applied to the asymmetric hydrocyanation of imines and the Mannich reaction.

Results and Discussion

Hydrocyanation of Imines (Strecker Reaction): Synthesis of the Catalyst

As was shown by Jacobsen et al.[2] 1,2-*trans*-diaminocyclohexane in combination with urea and thiourea functions[2,3] as hydrogen bridge-forming groups can furnish efficient organocatalysts suitable for enantioselective hydrogenation of imines (Strecker reaction). Optimized catalysts[3b,e] contain a salicylaldimine and a urea side-chain linked to the diaminocyclohexane backbone. Enantiomerically pure 1,2-*trans*-diaminocyclohexane is obtained from inexpensive mixtures of stereoisomeric 1,2-diaminocyclohexanes by resolution of their diastereomeric salts with tartaric acid. Nevertheless, enantiomerically pure glucosamine **1** which is readily accessible from chitin is considered an attractive alternative backbone structure for the construction of this type of catalysts. Due to its polyfunctionality, the carbohydrate can easily be modified in order to perform structure-efficiency relationship studies. By introduction of a second amino function, **1** offers four principal possibilities of arranging a Schiff base and a urea-derived side-chain as the optimal combination reported in the literature[3b,e] for enantioselective Strecker reactions (Figure 1).

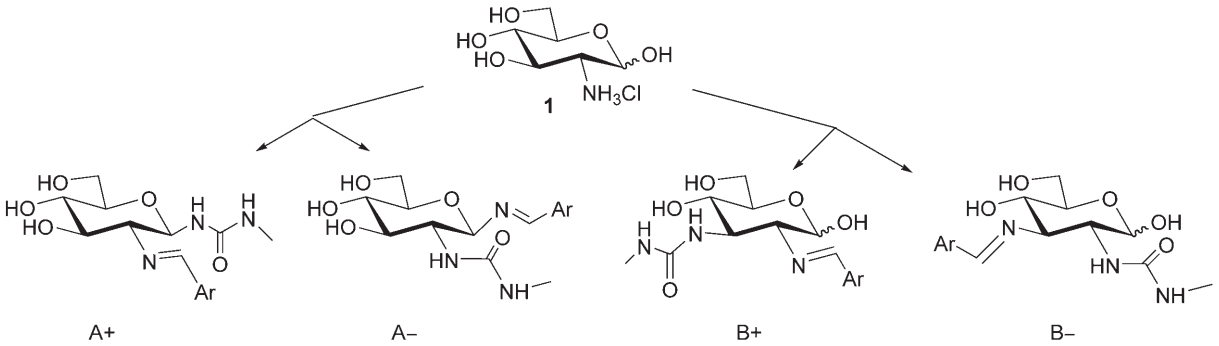
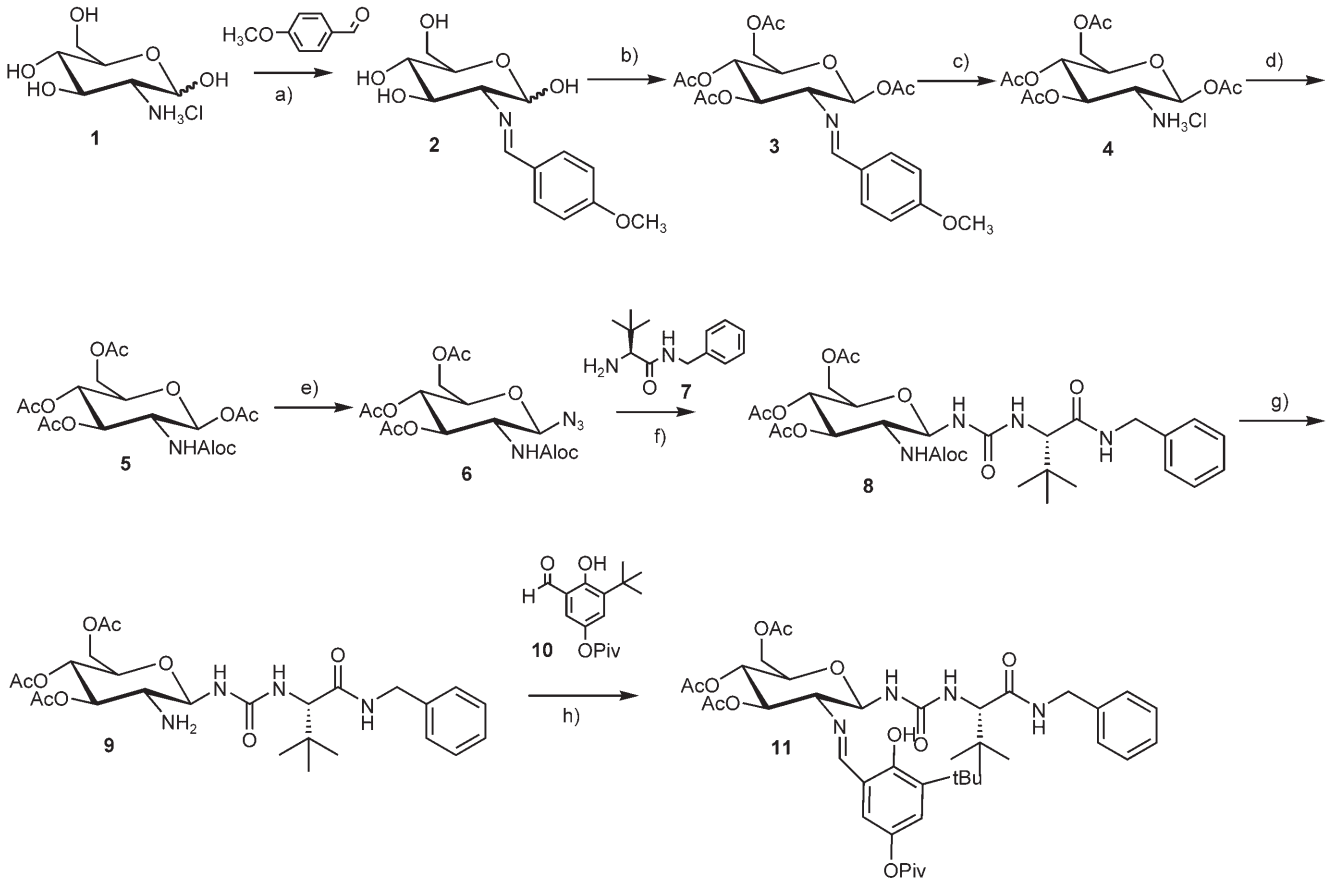


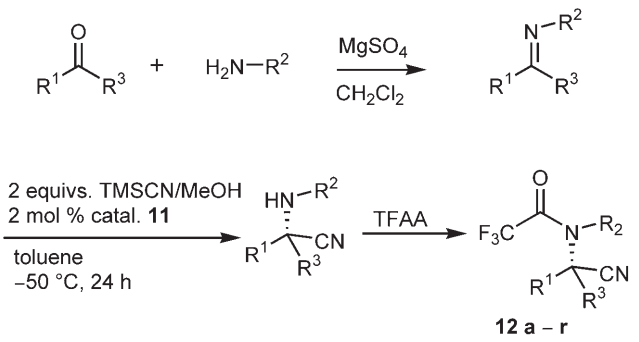
Figure 1. Possible Jacobsen-type organocatalysts not derived from 1,2-*trans*-diaminocyclohexane, but from D-glucosamine.



a) 1 N NaOH, 20 °C, 96%; b) Ac_2O, pyridine, 0 to 20 °C, 72%; c) 5.5 N HCl, acetone, Δ, 72%; d) AlocCl, $H_2O/CHCl_3$, $NaHCO_3$, 20 °C, 61%; e) TMSCN, $SnCl_4$, CH_2Cl_2, 20 °C, 89%; f) CO_2, PPh_3, DMF, 20 °C, 97%; g) $Pd(PPh_3)_4$, AcOH, Bu_3SnH, CH_2Cl_2, 20 °C; h) *i*-PrOH, $MgSO_4$, 20 °C, 92% (2 steps).

Scheme 1. Synthesis of the glucosamine-derived catalyst **11**.

In order to synthesize a type A+ catalyst, the amino function of D-glucosamine **1** was protected as the *p*-anisaldimine **2** which was acetylated to give compound **3** as the β-anomer. After acid-catalyzed hydrolysis of the imine, the allyloxycarbonyl (Aloc)[4] group was introduced into amine **4** to furnish allyl carbamate **5**.[5] Compound **5** is sufficiently stable to the conditions required for the $SnCl_4$-catalyzed reaction with trimethylsilyl azide[6] to give glycosyl azide **6**. Formation of the urea linkage with the L-*tert*-leucine benzylamide **7** was achieved by a Staudinger-aza-Wittig-type reaction according to Pintér[7] and yielded *N*-glycosylurea derivative **8**. Palladium(0)-catalyzed removal of the Aloc group to give **9** and condensation with salicylaldehyde derivative **10**[8] furnished the desired catalyst **11** (Scheme 1).



Scheme 2. Strecker reaction of aldimines catalyzed with glucosaminylurea derivative **11.**

Glucosaminylurea derivative **11** proved to be an efficient catalyst for the asymmetric hydrocyanation of a broad range of aldimines (Scheme 2 and Table 1).

As shown in Table 1, the Strecker reactions of aldimines of aromatic aldehydes (entries 1–14, 16, 18) proceeded with high yield and enantiomeric excess up to 84% at −50°C (not at −70°C as performed by Jacobsen et al.[3a]). Aliphatic aldimines (entry 15) or ketimines (entry 17) only reacted with moderate enantioselectivitiy. The electron-withdrawing *p*-nitro substituent (entry 11) gave rise to racemization of the formed nitrophenylglycinonitrile during the reaction. In the case of the reactive furfuryl derivative (entry 12), the non-catalyzed transformation took place to a perceptible extent resulting in a moderate enantiomeric excess of only 50%.

In the Strecker reaction of benzaldimine **12r** at −70°C under conditions applied by Jacobsen et al.[3a] high yield and an excellent enantioselectivity of 95% was achieved with the glucosamine-derived catalyst **11** (Table 2, entry 1)

Table 2. The results for the asymmetric Strecker reaction to give **12r** with different catalysts.

Entry	Catalyst	*T*	Yield of **12r** [%]	*ee* [%][a,d]
1	**11** (2 mol%)	−70°C	86	95 (*S*)
2	**13** (5 mol%)	−70°C	100[b]	15[c] (*S*)
3	**14** (4 mol%)	−50°C	64	30 (*S*)
4	**15** (2 mol%)	−50°C	85	23 (*R*)
5	**16** (8 mol%)	−50°C	35	12 (*R*)
6	**17** (4 mol%)	−50°C	30	15 (*S*)
7	**18** (2 mol%)	−70°C	45	36 (*S*)
8	**19** (8 mol%)	−50°C	54	4 (*S*)
9	**20** (2 mol%)	−70°C	18	10 (*S*)

[a] Determined by HPLC analysis using commercial chiral columns.
[b] Determined after 24 h by ^{1}H NMR.
[c] Determined by optical rotation and comparison with the literature.[3a)]
[d] Assignment of the absolute configuration based on the literature.[3a)]

Strecker Reaction: Structural Variations of the Catalyst

Effects of structural variations of catalyst **11** on the enantioselectivity of the Strecker reaction were investigated with nine representative compounds (Figure 2). Structure modifications concerned the position of the functional side-chains (Figure 2, **13**, **14**, **15**) and alterations of the protecting group pattern of

Table 1. The results of the enantioselective Strecker reaction with various aldimines.

Entry	Product	R^1	R^2	R^3	Yield [%]	*ee* [%][a]
1	**12a**	2-Me-C_6H_4	allyl	H	81	69
2	**12b**	3-Me-C_6H_4	allyl	H	93	78
3	**12c**	4-Me-C_6H_4	allyl	H	83	75
4	**12d**	2-MeO-C_6H_4	allyl	H	98	64
5	**12e**	3-MeO-C_6H_4	allyl	H	96	66
6	**12f**	4-MeO-C_6H_4	allyl	H	79	82
7	**12g**	2-Br-C_6H_4	allyl	H	69	72
8	**12h**	3-Br-C_6H_4	allyl	H	83	74
9	**12i**	4-Br-C_6H_4	allyl	H	77	84
10	**12j**	4-*t*-Bu-C_6H_4	allyl	H	82	84
11	**12k**	4-NO_2-C_6H_4	allyl	H	67	0
12	**12l**	2-furfuryl	allyl	H	87	50
13	**12 m**	1-naphthyl	allyl	H	78	80
14	**12n**	2-naphthyl	allyl	H	73	76
15	**12o**	cyclohexyl	benzyl	H	60	47
16	**12p**	6,7-dimethoxyisoquinoline		H	97	86
17	**12q**	Ph	4-Br-$C_6H_4CH_2$	Me	63	50
18	**12r**	Ph	allyl	H	72	84

[a] Determined by HPLC analysis using commercial chiral columns.

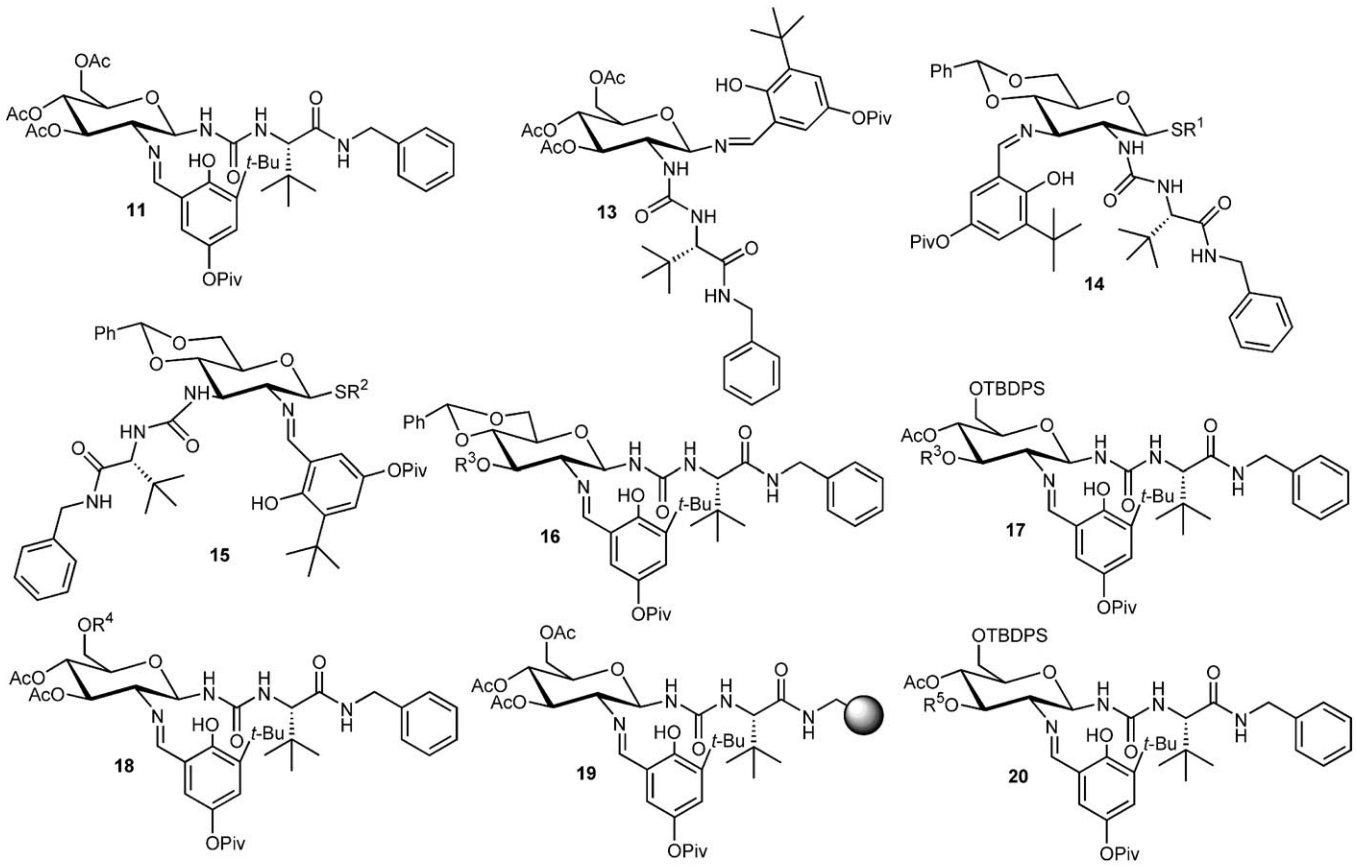
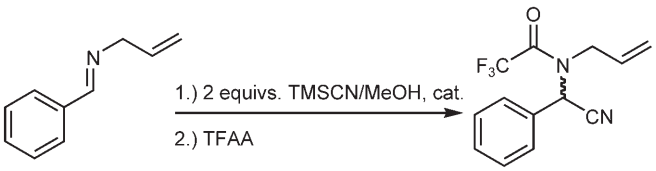


Figure 2. Varied organocatalysts based on glucosamine.

the carbohydrate scaffold (Figure 2, **16**, **17**, **18**, **20**) as well as immobilization of the catalyst on a solid support (Figure 2, **16**, **17**, **19**).

Compound **13** was synthesized from **1** by forming its *p*-nitrophenoxycarbonyl derivative prior to the introduction of the anomeric azido group.[9] The 2,3-diaminoglucose derivatives **14** and **15** were formed from the 3-azido precursor obtained by a double inversion of configuration at position 3 of the corresponding glucosamine derivative.[10] For the formation of the compounds modified in the carbohydrate protecting group pattern, compound **8** was deacetylated by Zemplén transesterification. The product deblocked at the hydroxy functions was subjected to appropriate protecting group manipulations and immobilization reactions.[11] The results of enantioselective Strecker reactions catalyzed by **11** and its variants **13**–**20** are summarized in Scheme 3 and Table 2.

Reversal of the localization of the functional side-chains in glucosaminylamine catalyst **11** leads to catalyst **13**. However, its use in the Strecker reaction under identical conditions (Table 2, entries 1 and 2) resulted in a tremendous decrease of enantioselectivity.



Scheme 3. Strecker synthesis of amino nitrile **12r** catalyzed by varied glucosamine-derived catalysts.

The anticipated inverse induction of the aminonitrile configuration was not observed. This result gives evidence that the carbohydrate is not just a cyclohexane surrogate. The *exo*-anomeric effect, that is, the delocalization of π-electrons of the nitrogen substituent in the anomeric position, in **11** enhances the NH-acidity. In **13**, however, it reduces the electron density of the imine nitrogen (Figure 3) and its ability to form a hydrogen bond to the phenol hydroxy group which spatially fixes the salen structure.

Moving the functional side chains from the 1,2 position (**11**) to the 2,3 position resulted in a catalyst **14** which also induced prevailing formation of (*S*) aminonitrile **12r**, however, with distinctly lower enantiose-

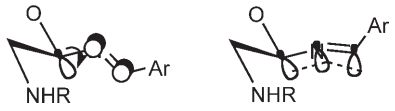
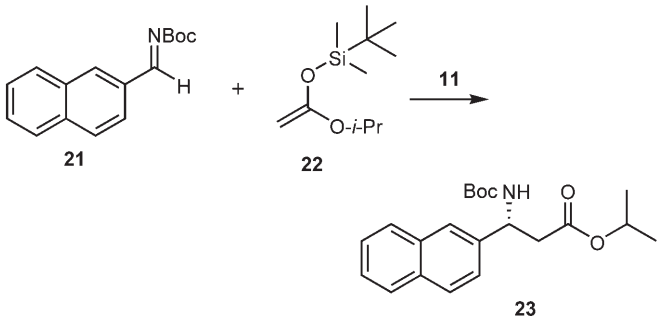


Figure 3. Effect of π-electron delocalization on the electron density of the imine in catalyst **13**.

lectivity. In compound **15** the urea-type and the salen side-chains are in reversed positions. This catalyst induced opposite enantioselectivity (entry 4), but again with low efficiency. The moderate selectivity presumably also arises from the diminished flexibility of **14** and **15** due to the benzylidene acetal in position 4 and 6 of the carbohydrate which constitutes a rigid heterodecaline framework.

The very subtle influence of substituents at the carbohydrate even of those quite remote from the catalytic centre on the enantiodifferentiating potency of the catalysts is illustrated in Strecker reactions catalyzed by compounds **16**–**20** (Table 2, entries 5–9). The use of catalysts with larger protecting groups and introduction of linkers (**18**, **20**) instead of the *O*-acetyl groups resulted in a dramatic decrease of enantioselectivity. Immobilization on polystyrene[12] either *via* the carbohydrate (**16**, **17**) or *via* the amino acid amide (**19**) yielded catalysts which displayed low enantioselectivity. Obviously, these modifications in the protecting group pattern force the carbohydrate scaffold to adopt a less favorable conformation. None of these modified catalysts **13**–**20** reached the high efficiency of Jacobsen's catalyst.[3a,b] or of the organocatalyst **11** derived from the glucosaminyl azide. In compound **11**, an enhanced NH acidity may compensate the restricted conformational flexibility compared to the diaminocyclohexane-derived catalyst. As a consequence, this compound is a potent enantioselective catalyst of the Strecker reaction. Altogether, the obtained results suggest that the polar functions within the carbohydrate interfere with the enantioselectivity of the reaction by offering too many basic centers for interaction with HCN. In Jacobsen's catalyst such an interaction is restricted to the catalytic centre. The only improving effect by the carbohydrate may lie in the higher NH acidity provided the urea function is in anomeric position as given in **11**.



Scheme 4. Mannich reaction catalyzed by glcosamine-derived catalysts **11**.

Enantioselective Catalysis of the Mannich Reaction

Like α-amino acids generated by the Strecker reaction, β-amino acid derivatives accessible, for example, *via* Mannich reactions are important building blocks for the construction of pharmaceutical products and natural compounds. Therefore, enantioselective syntheses of these compounds are of interest.[3c,13] Jacobsen et al.[3c] successfully applied their 1,2-diaminocyclohexane-derived catalyst to enantioselective Mannich reactions. Glucosaminylamine-derived catalyst **11** proved also efficient in the enantioselective catalysis of the Mannich reaction between aldimine **21** and silyl ketene acetal **22** (Scheme 4).

The reaction conditions were optimized with regard to temperature, solvent, equivalents of the enolate (**22**) and concentration of the reaction solution. At −20 °C, the yield of β-amino acid ester **23** was satisfying (Table 3). The excess of enantiomer remained moderate (about 50 %). In contrast to the results ob-

Table 3. Conditions and results of the enantioselective Mannich reaction with catalyst **11**.

Entry	mol % of 11	*T*	Solvent	*c* [mol·L^{-1}]	Equivs. of **22**	Yield [%][a]	*ee* [%][b]
1	5	−40 °C	toluene	0.15	2	12	48
2	5	−20 °C	toluene	0.15	2	59	50
3	5	−20 °C	toluene	0.40	2	53	48
4	5	−20 °C	toluene	0.004	2	49[c]	54
5	2	−20 °C	toluene	0.15	2	62	48
6	10	−20 °C	toluene	0.15	2	73	58
7	5	−20 °C	toluene	0.15	1.1	76	54
8	5	−20 °C	THF	0.15	1.1	68	12
9	5	−20 °C	CH_2Cl_2	0.15	1.1	51	0

[a] Yield after 48 h.
[b] Determined by HPLC analysis using commercial chiral columns.
[c] Yield after 96 h.

tained by Jacobsen, lowering the temperature below −20 °C did not improve the enantioselectivity. Best results were obtained in toluene. In more polar solvents low or no enantioselectivity was observed. The decreased enantioselectivity of the Mannich reaction compared to the Strecker reaction may be traced back to the reduced basicity of the *N*-acylimine **21** which reduces its affinity to the urea NH groups obviously essential for binding the substrate to the catalyst. After all, the mode of action of the catalyst which could explain the observed effects of structure variation remains unclear.

Conclusions

Efficient organocatalysts for enantioselective Strecker and Mannich reactions can by constructed from D-glucosamine as a component of the natural chiral pool. High enantioselectivity in Strecker reactions was only achieved with the glucosaminylurea derivative **11** carrying the salen side-chain in the 2-position. With this catalyst high yield and enantioselectivity up to 95% were accomplished in hydrocyanation reactions of aromatic aldimines. The glucosamine derivative **11** proved also able to enantioselectively catalyze the Mannich reaction of *N*-Boc-aldimine **21** with silyl ester enolate **22** to furnish β-amino acid ester **23** with yields up to 76% and an enantiomeric excess up to 58%. Even slight modification of the carbohydrate-derived catalyst's architecture decreased the enantioselectivity of the investigated reactions giving evidence of the fact that the polar nature of the carbohydrate backbone obviously does not favor enantiodifferentiation in these addition reaction of nucleophiles to imines.

Experimental Section

General Procedure for the Preparation of Substrate Imines

To a suspension of 3 equivalents of $MgSO_4$ in dry CH_2Cl_2 equimolar amounts of aldehyde and amine are added and stirred at room temperature for 20 h. After filtering off the $MgSO_4$, the solvent is evaporated affording the desired product in pure form and in quantitative yield.

General Procedure for the Preparation of *N*-Substituted α-Aminonitriles 12

To dry toluene (4 mL) TMSCN (0.58 mL, 4.35 mmol) is added and the solution is cooled to 0 °C. After addition of dry methanol (0.86 mL), the solution is stirred at 0 °C for 1 h. The chosen amount of catalyst and the respective imine (0.5 mmol) are dissolved in dry toluene (6 mL) and cooled to the desired reaction temperature. The cyanide solution (1.27 mL, 1 mmol TMSCN) is added slowly *via* syringe and the reaction mixture is stirred for 24 h. After addition of trifluoroacetic anhydride (0.15 mL, 1 mmol), the solution is warmed to room temperature and stirred for additional 3 h. After evaporation of the solvent under vacuum the remaining oil is purified by flash chromatography on silica gel.

1,3,4,6-Tetra-*O*-acetyl-β-D-glucosamine Hydrochloride (Ac_4GlcNH_2·HCl) (4)

The product was obtained following a known procedure[14].

1,3,4,6-Tera-*O*-acetyl-2-*N*-(allyloxycarbonyl)-2-amino-2-deoxy-β-D-glucopyranose [$Ac_4GlcN(Aloc)$] (5)

1,3,4,6-Tetra-*O*-acetyl-β-D-glucosamine hydrochloride[14] (**4**) (20.0 g, 52.1 mmol) is dissolved in water (200 mL) and $NaHCO_3$ (16.8 g, 200 mmol) is added. To this vigorously stirred mixture, a solution of allyl chloroformate (8.30 mL, 78.2 mmol) in chloroform (200 mL) is slowly added drop wise under stirring. After 4 h the layers are separated and the watery phase is extracted twice with chloroform (50 mL each). The combined organic layers are washed with water (100 mL) and with brine (100 mL). After drying over $MgSO_4$ the solvent is removed and the resulting viscous oil is purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:5→5:1) affording the product as a colorless, amorphous solid; yield: 18.5 g (82%); $R_f = 0.48$ (CH_2Cl_2/EtOAc, 5:1); $\alpha]_D^{20}$: 16.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.89–5.80$ (m, 1H, -CH_2-C*H*=CH_2), 5.67 (d, J = 8.8 Hz, 1H, H-1), 5.25–5.00 (m, 4H, -CH_2-CH=CH_2, H-3, H-4), 4.52 (d, J = 4.1 Hz, 2H, -CH_2-CH=CH_2), 4.25 (dd, J = 4.8 Hz, J = 12.5 Hz, 1H, H-6), 4.08 (dd, J = 1.8 Hz, J = 12.5 Hz, 1H, H-6′), 3.96–3.86 (m, 1H, H-2), 3.82–3.77 (m, 1H, H-5), 2.08, 2.05, 2.01, 2.00 (s, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 170.8$, 170.6, 169.4 (*C*OOCH$_3$), 155.6 (OCONH), 132.5 (-CH_2-*C*H=CH_2), 117.7 (-CH_2-CH=*C*H_2), 93.2 (C-1), 73.3 (C-3), 73.0 (C-5), 72.8 (-*C*H_2-CH=CH_2), 68.1 (C-4), 61.9 (C-6), 54.9 (C-2), 20.8, 20.7, 20.6, 20.5 (CH_3); anal. calcd. for $C_{14}H_{20}O_8N_4$: C 50.10, H 5.84, N 3.25; found: C 49.95, H 6.07, N 3.28.

3,4,6-Tetra-*O*-acetyl-2-*N*-(allyloxycarbonyl)-2-amino-2-deoxy-β-D-glucopyranosyl Azide [$Ac_3GlcN(Aloc)N_3$] (6)

1,3,4,6-Tera-*O*-acetyl-2-*N*-(allyloxycarbonyl)-2-amino-2-deoxy-β-D-glucopyranose (**5**) (17.3 g, 40.1 mmol) is dissolved in dry CH_2Cl_2 (300 mL). To this solution trimethylsilyl azide (8.0 mL, 61.1 mmol) and tin(IV) chloride (0.87 mL, 6.4 mmol) are added *via* syringe at room temperature, and the mixture is stirred for 4 h. The solution is poured into a saturated $NaHCO_3$ solution (300 mL) and shaken in a separatory funnel until evolution of CO_2 ceases. The organic layer is separated, washed with brine (200 mL) and dried over $MgSO_4$. After removal of the solvent, the resulting viscous oil is purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 5:1) affording a colorless, amorphous solid; yield: 14.1 g (85%); $R_f = 0.52$ (CH_2Cl_2/EtOAc 5:1); $\alpha]_D^{20}$: −22.5 (*c* 1, CH_2Cl_2); FT-IR (CH_2Cl_2 thin film): ν = 3053 (s, ν CH), 2973 (s, ν CH), 2117 (s, ν N_3), 1746 (s, ν CO), 1520 cm^{-1} (m, ν NCOO); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.97–5.77$ (m, 1H, -CH_2-C*H*=CH_2), 5.30–5.17 (m, 3H, -CH_2-CH=CH_2, NH), 5.10–4.99 (m, 2H, H-3, H-4), 4.77 (d, J = 8.8 Hz,

1H, H-1), 4.55 (d, $J=5.4$ Hz, 2H, -C*H*-CH=CH_2), 4.25 (dd, $J=4.6$ Hz, $J=12.2$ Hz, 1H, H-6), 4.12 (dd, $J=2.3$ Hz, $J=12.2$ Hz, 1H, H-6′), 3.81–3.72 (m, 1H, H-5), 3.58 (q, $J=9.8$ Hz, 1H, H-2), 2.07, 2.01, 2.00 (s, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=170.6$, 169.3 (*C*OOCH_3), 155.5 (OCONH), 132.3 (-CH_2-*C*H=CH_2), 118.0 (-CH_2-CH=*C*H_2), 88.7 (C-1), 74.0 (C-3), 72.0 (C-5), 68.2 (C-4), 66.1 (-*C*H_2-CH=CH_2), 61.9 (C-6), 55.8 (C-2), 20.7, 20.6 (CH_3); FD-MS: $m/z=415.9$ (55%) $[M+H]^+$, 414.9 (18%) $[M]^+$, 372.8 (7%) $[M-N_3]^+$.

N-[3,4,6-Tri-*O*-acetyl-2-*N*-(allyloxycarbonyl)-2-amino-2-deoxy-β-D-glucopyranosyl]-carbamoyl-L-*tert*-leucinyl-benzylamide (8)

L-*tert*-Leucine-*N*-benzylamide (**7**) (1.19 g, 5.42 mmol) is dissolved in dry DMF (30 mL) and the solution is saturated with dry CO_2. Under a constant stream of CO_2 a solution of 3,4,6-tetra-*O*-acetyl-2-*N*-(allyloxycarbonyl)-2-amino-2-deoxy-β-D-glucopyranosyl azide (**6**) (2.16 g, 5.21 mmol) in dry DMF (5 mL) is added. After 2 min a solution of triphenylphosphine (1.49 g, 5.68 mmol) in dry DMF (10 mL) is slowly added while CO_2 is constantly bubbled through the solution. After 7 h the solvent is removed and the resulting viscous oil is purified by column chromatography on silica gel ($CHCl_3$/acetone 10:1) affording a colorless, amorphous solid; yield: 3.11 g (94%); $R_f=0.29$ ($CHCl_3$/acetone 10:1); $\alpha]_D^{20}$: 16.6 (*c* 2, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=$ 8.59 (t, $J=5.8$ Hz, 1H, -N*H*-CH_2Ph), 7.44 (d, $J=9.8$ Hz, 1H, -N*H*-COO-), 7.31–7.21 (m, 5H, arom), 6.88, 6.64 (d, $J=$ 9.8 Hz, 1H, -N*H*-CO-N*H*-), 5.88–5.81 (m, 1H, -CH_2-C*H*=CH_2), 5.20–5.11 (m, 2H, -CH_2-CH=CH_2), 5.05 (t, $J=9.8$ Hz, 1H, H-3), 4.96 (t, $J=9.8$ Hz, 1H, H-1), 4.80 (dd, $J=9.8$ Hz, $J=9.4$ Hz, 1H, H-4), 4.51 (dd, $J=5.0$ Hz, $J=14.1$ Hz, 1H, -CH_2-CH=CH_2), 4.40 (dd, $J=4.9$ Hz, $J=14.1$ Hz, 1H, -CH_2-CH=CH_2), 4.32 (dd, $J=6.2$ Hz, $J=14.9$ Hz, 1H, H-6), 4.24–4.13 (m, 2H, H-6′, -CH_2-NHCH_2Ph), 4.06 [d, $J=9.7$ Hz, 1H, -C*H*$(CH_3)_3$], 3.88–3.85 (m, 1H, -CH_2-NHCH_2Ph), 3.70–3.67 (m, 1H, H-5), 3.49 (q, $J=9.9$ Hz, 1H, H-2), 1.97, 1.94, 1.89 (s, 3H, -OCOCH_3), 0.84 [s, 9H, -CHC(CH_3)$_3$]; ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta=170.7$, 169.9, 169.4, 169.2 (-O*C*OCH_3, -CONH-), 156.3 (-NHCONH-), 155.8 (-NHCOO), 139.2 (C arom), 133.4 (-CH_2-*C*H=CH_2), 128.1, 127.4, 126.7 (C arom), 116.6 (-CH_2-CH=*C*H_2), 79.9 (C-1), 73.7 (C-3), 71.6 (C-5), 68.6 (C-4), 64.3 (-*C*H_2-CH=CH_2), 61.9 (C-6), 59.9 [-*C*HC$(CH_3)_3$], 54.3 (C-2), 42.0 (-NH*C*H_2Ph), 34.4 [-CH*C*$(CH_3)_3$], 26.4 [-CHC(*C*H_3)$_3$], 20.4, 20.3 (-OCO*C*H_3); FD-MS: $m/z=635.2$ (25%) $[M+H]^+$, 246.8 (5%) [hydantoin]$^+$; anal. calcd. for $C_{30}H_{42}O_{11}N_4$: C 56.77, H 6.67, N 8.83; found: C 56.81, H 7.70, N 8.76.

5-*tert*-Butyl-3-pivaloyloxy-salicylaldehyde (10)

The product was obtained following a known procedure.[8]

N-[3,4,6-Tri-*O*-acetyl-2-*N*-(3′-*tert*-butyl-2′-hydroxy-5′-pivaloyloxybenzylidene)-2-amino-2-deoxy-β-D-glucopyranosyl]-carbamoyl-L-*tert*-leucinyl-benzylamide (11)

To a solution of (**8**) (313 mg, 493 μmol) in CH_2Cl_2 (10 mL) $Pd(PPh_3)_4$ (11 mg, 9.4 μmol) is added. Quickly one after the other, glacial acetic acid (67 μl, 1.18 mmol) and tri-*n*-butyltin hydride (0.15 mL, 543 μmol) are added and the mixture is stirred at room temperature for 30 min. After evaporation of the solvent, the residue is co-evaporated twice with toluene (10 mL each). The resulting oil is dissolved in isopropanol (10 mL). To this solution $MgSO_4$ (30 mg) and 5-*tert*-butyl-3-pivaloyloxy-salicylaldehyde[8] (**10**) (152 mg, 543 μmol) are added. The suspension is heated to 80 °C for 2 h. After filtering off the $MgSO_4$ the solvent is removed under vacuum. The resulting viscous oil is purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 4:1) affording a yellow solid; yield: 366 mg (92%); $R_f=0.29$ (CH_2Cl_2/EtOAc 4:1); $\alpha]_D^{20}$: 19.1 (*c* 1, CH_2Cl_2); FT-IR (CH_2Cl_2 thin film): ν=3341 (br, ν OH), 2986 (s, ν CH), 1748 (s, ν O*CO*CH_3), 1675 (br, ν NH*CO*NH), 1525 cm^{-1} (br, ν *NHCONH*); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=13.29$ (s, 1H, OH), 8.52–8.49 (t+s, $J=5.5$ Hz, 2H, -C*H*=N-, -N*H*CH_2Ph), 7.17–7.13 (m, 5H, arom), 7.10 (d, $J=2.8$ Hz, 1H, arom), 6.96–6.94 (m, 2H, arom, -N*H*-CO-NH), 6.28 (d, $J=9.6$ Hz, 1H, -NH-CO-N*H*), 5.48 (t, $J=9.5$ Hz, 1H, H-3), 5.36 (t, $J=9.5$ Hz, 1H, H-1), 4.92 (t, $J=9.5$ Hz, 1H, H-4), 4.27–4.20 (m, 2H, H-6, -NHCH_2Ph), 4.11–4.10 (m, 1H, H-5), 4.09–4.07 [m, 1H, -C*H*C$(CH_3)_3$], 4.04 (dd, $J=2.0$ Hz, $J=$ 12.3 Hz, 1H, H-6′), 3.42 (t, $J=9.5$ Hz, 1H, H-2), 1.99, 1.97, 1.86 (s, 3H, -OCOCH_3), 1.33 [s, 9H, -OCOC$(CH_3)_3$], 1.28 [s, 9H, -C$(CH_3)_3$], 0.83 [s, 9H, -CHC(CH_3)$_3$]; ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta=170.5$, 169.9, 169.4, 169.1, 168.7 [-O*C*OCH_3, -*C*ONHCH_2Ph, -O*C*OC$(CH_3)_3$], 157.1 (-CH= N-), 156.0 (-NHCONH-), 141.7, 139.1, 137.7, 123.3, 122.2 [C-(quart)], 128.0, 127.3, 126.6, 117.2 (C arom), 79.9 (C-1), 73.3 (C-3), 71.6 (C-5), 70.9 (C-2), 68.2 (C-4), 62.0 (C-6), 59.8[-*C*HC$(CH_3)_3$], 42.0 (-NH*C*H_2Ph), 38.4 [-OCO*C*$(CH_3)_3$], 34.5 [-CH*C*$(CH_3)_3$], 28.9 [-*C*$(CH_3)_3$], 26.7 [-OCOC(*C*H_3)$_3$], 26.4 [-CHC(*C*H_3)$_3$], 20.5, 20.4, 20.2 (-OCO*C*H_3); FD-MS: $m/z=$ 811.8 (91%) $[M+H]^+$; anal. calcd. for $C_{42}H_{58}O_{12}N_4$: C 62.21, H 7.21, N 6.91; found: C 61.85, H 7.23, N 6.72.

Typical Procedure for the Catalyzed Mannich Reaction: 3-*tert*-Butyloxycarbonylamino-3-(2-naphthyl)-isopropyl Propionate (23)

A solution of **21** (29 mg, 114 μmol) and catalyst **11** (e.g., 5 mol%: 4.6 mg, 5.7 μmol) in dry toluene (e.g., $c=0.15$ mol·L^{-1}: 0.8 mL) is cooled to the desired reaction temperature. Over a period of 10 min, *via* syringe, **22** (e.g., 1.1 equivs., 27 mg, 125 μmol) is added, and the reaction mixture is stirred for 48 h at the respective reaction temperature. After evaporation of the solvent, the residue is purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:10); $R_f=0.23$ (EtOAc/cyclohexane 1:10) to give **23** (see Table 3).

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