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PAPER

Novel carbohydrate-based bifunctional organocatalysts for nucleophilic addition to nitroolefins and imines†

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Glucosamine has been selected as a cheap and readily available chiral scaffold for the synthesis of a series of novel enantiomerically pure bifunctional organocatalysts bearing a tertiary amino group in proximity to a (thio)urea group. The catalytic behaviour of these compounds, both as neutral and *N*-protonated species, was investigated using the addition of acetylacetone to β-nitrostyrene as a model reaction. Under optimized experimental conditions, chemical yields up to 93% and enantioselectivities up to 89% were obtained. Semiempirical (AM1) computational studies allowed to find a theoretical rationale for the chemical and stereochemical behaviour of the catalyst of choice. These catalysts were also preliminarily investigated as promoters in the addition of diethyl malonate to the *N*-Boc imine of benzaldehyde, affording the product in up to 81% ee.

Introduction

The development of new and efficient chiral catalytic systems represents a tumultuously expanding area in present day organic chemistry. In particular, the design of chiral efficient multifunctional organocatalysts has received a great deal of attention.[1] Several approaches to achieve this goal were inspired by Nature's extraordinarily efficient enzyme-catalyzed transformations, in which multistep processes are readily performed, in sharp contrast to the lengthy and tedious procedures of organic synthesis. The key elements that are able to guarantee enzymes' extraordinary efficiency are poly-functionalization, pre-organization and co-operativity. Like many other groups, we have been actively engaged in the attempt to reproduce Nature's efficiency in performing catalytic transformations by building new bifunctionalized chiral catalysts, where two organic residues will co-operate to promote stereoselective reactions and thus perform as polyfunctional, synergic organocatalysts.[2] Examples of highly successful catalytic systems developed in the last few years are bifunctional (thio)urea–tertiary amine organocatalysts, employed in a great variety of stereoselective transformations.[3]

In this context, however, it must be noted that only a very limited set of chiral scaffolds have been used for the construction of such catalytic systems, which were mostly derived from 1,2-diamino cyclohexane, cinchona alkaloids, and 1,1′-binaphthyl 2,2′-diamine. Since all of these scaffolds have some drawbacks, mostly in term of cost and the necessity of complex synthetic manipulation, the search for alternative chiral structures suitable for the design of novel multifunctional organocatalysts is still a topic of front-line interest.

Carbohydrates are primarily involved in inflammatory processes, bacterial and viral invasions, tumour growth and metastasis, and many other crucial biological events.[4] Due to their enormous structural diversity, oligo- and polysaccharides play a fundamental role in signal transduction and vital molecular recognition phenomena, thus offering exciting new therapeutic opportunities in biomedical fields.[5] Due to their crucial biological roles carbohydrates, especially mono- and disaccharides, possess a unique set of chemical and structural features that make them particularly attractive as molecular scaffolds. They are readily available in a variety of diastereomeric forms, chiral and conformationally rigid molecules providing a well defined three-dimensional spatial arrangement of substituents and various multi-configured hydroxyl groups for chemical modification. We therefore reasoned that carbohydrates could offer extraordinary possibilities as basic structures onto which new metal-free catalysts can be developed, for their low cost, potential polyfunctionalization, and easy possibility of different modifications for fine tuning of steric, electronic and solubility properties. To the best of our knowledge, there is only one report describing the use of D-glucosamine as starting material for the synthesis of a new class of bifunctional catalysts able to promote the Strecker and Mannich reaction with imines.[6] In this pioneering work Kunz *et al.* explored the preparation of carbohydrate-based organocatalysts, where the

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† Electronic supplementary information (ESI) available: Synthesis and characterization of bifunctional catalysts **13** and **16**. Characterization details of bifunctional catalysts **10**, **12**, and **14**. Copies of ^{1}H and ^{13}C NMR spectra of compounds **3**, **7**, **10**–**14**, and **16**. ^{1}H-NMR spectra and HPLC chromatograms on chiral stationary phase of the products of the catalytic addition of acetylacetone to different nitrostyrenes and of diethyl malonate to imines. See DOI: 10.1039/c0ob01240h

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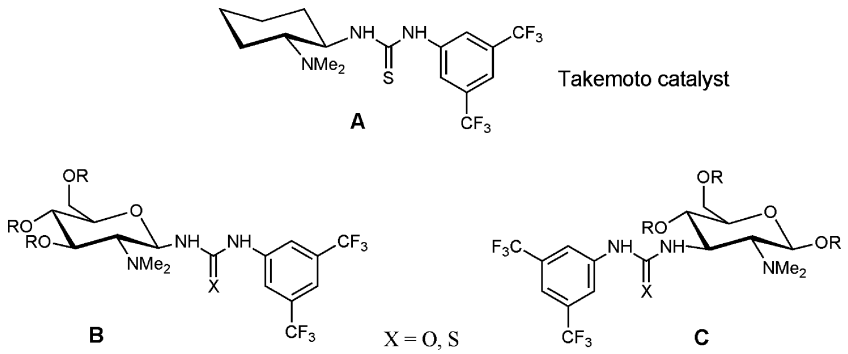

Fig. 1 Novel saccharide-based chiral bifunctional organocatalysts.

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monosaccharide effectively replaced the more frequently used 1,2-diamino cyclohexane scaffold and was the only stereocontrolling element present in the molecule.[7]

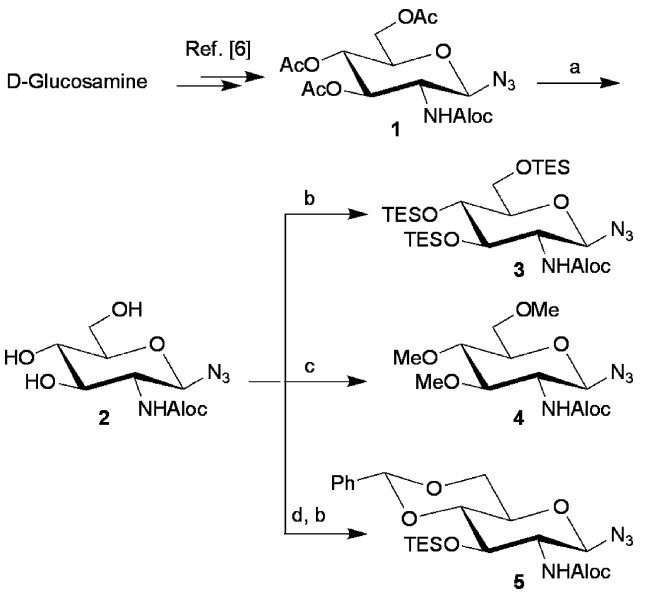
More recently, a few contributions have explored the use of saccharide-substituted chiral thiourea–amine compounds as promoters of stereoselective Michael additions to nitroolefins,[8] and aza-Henry reactions.[9] It must be noted, however, that in these catalysts either the chiral 1,2-diamino cyclohexane or other amino acid-derived enantiopure diamine scaffolds were retained as the crucial element for the stereocontrol of the reaction, while carbohydrates have, in all cases, been introduced only as an additional element possibly useful for a fine tuning of the catalytic properties of the molecule.

Based on these considerations and inspired by the seminal work by Kunz *et al.*,[6] we decided to investigate the synthesis of a new family of (thio)urea–amine organocatalysts,[10] where both catalytic residues were connected by an enantiomerically pure saccharide-based scaffold, as an alternative chiral skeleton to diamino cyclohexane (Fig. 1).

Results and discussion

When designing the novel metal-free catalysts, we selected as a starting material the cheap, readily available in large quantities D-glucosamine, which, by introduction of a second amino function, allows the construction of a bifunctional amine–(thio)urea-containing catalyst. Its polyfunctionalization offers several possible structural modifications to be explored for the development and fine tuning of the novel enantiomerically pure organocatalysts (Fig. 1).

The bifunctional catalysts of type **B** were synthesized according to the following strategy (Scheme 1). First, commercial D-glucosamine was converted into the 1-azido-2-*N*-allyloxycarbonyl derivative **1** as previously described.[6] Next, Zemplèn *O*-deacetylation of glycosyl azide **1** provided **2**, and the 3, 4, and 6-hydroxyls were suitably functionalised with various protecting groups, in order to modulate the polarity, the rigidity and the hydrogen-bonding ability of the saccharide scaffold, and to evaluate their influence on the behaviour of the resulting organocatalysts. Accordingly, the highly polar *O*-acetylated scaffold **1**, and its deacetylated derivative **2**, both suitable to act as hydrogen-bonding acceptors, were employed for the synthesis of organocatalysts **10** and **13**, respectively. On the other hand, silyl and alkyl ether protecting groups dampen the polarity of



Scheme 1 The synthesis of glycosyl azides. (a) NaOMe, MeOH (qu.); (b) TESOTf, *sym*-collidine, DMF (**3**: 97%, **5**: 97% over 2 steps); (c) MeI, NaH, DMF (82%); (d) $PhCH(OMe)_2$, (+)-β-camphorsulfonic acid, $CHCl_3$ (qu). TES = triethylsilyl.

the saccharide scaffold and might interfere with its hydrogen-bonding capacity. Intermediate **2** was therefore converted into **3** by treatment with triethylsilyl trifluoromethanesulfonate in the presence of *sym*-collidine (Scheme 1).

Moreover, since semiempirical calculations suggested that the steric hindrance of the substituents on the glycosyl moiety may play a crucial role in the catalytic activity, small size alkyl ethers, such as methyl groups were introduced on **2** under classical Williamson conditions to afford **4**. Finally, the importance of the rigidity of the saccharide scaffold was investigated with the preparation of glycosyl azide **5** by introduction of the 4,6-*O*-benzylidene acetal followed by 3-*O*-silylation (Scheme 1).

Having the properly protected saccharide scaffolds in our hands, we approached their conversion into bifunctional organocatalysts of type **B** reported in Fig. 2. Preliminary investigations suggested that the best sequence was the initial installation of the (thio)ureido linkage, followed by the generation of the tertiary amine. Since our aim was to mimic the Takemoto catalyst (**A** in Fig. 1), glycosyl azide **1** was reacted with triphenylphosphine followed by the addition of 3,5-bis-trifluoromethyl phenylisothiocyanate (Scheme 2).

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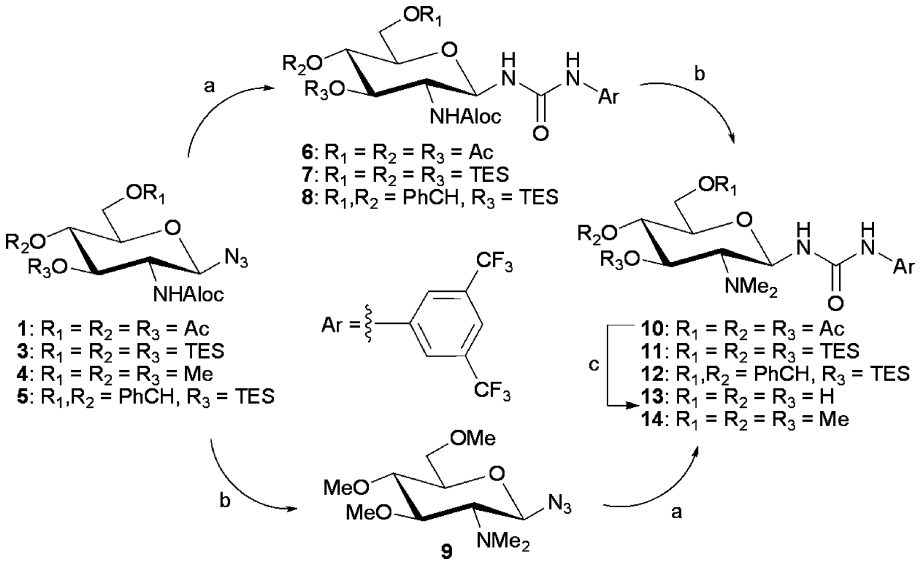


Scheme 2 The synthesis of glucosaminylurea-based organocatalysts. (a) PPh_3, ArNCS, THF (**6**: 45%, **7**: 60%, **8**: 36%, **14**: 71%); (b) $Pd(PPh_3)_4$, Bu_3SnH, AcOH, CH_2Cl_2, then HCHO, $NaCNBH_3$, THF (**9**: 67%, **10**: 52%, **11**: 47%, **12**: 61%); (c) NaOMe, MeOH, (qu).

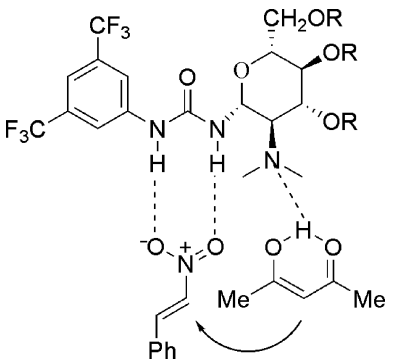
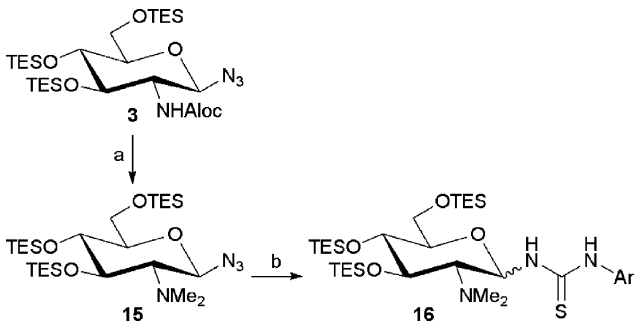


Fig. 2 The proposed stereoselection model for acetylacetone addition to *β*-nitrostyrene.



Scheme 3 Synthesis of glucosaminylthiourea organocatalyst **16**. (a) $Pd(PPh_3)_4$, Bu_3SnH, AcOH, CH_2Cl_2, then HCHO, $NaCNBH_3$, THF (57%); (b) H_2, Pd/C, ArNCS, THF (46%).

We observed the exclusive generation of the urea-linked compound **6**, which was confirmed by NMR spectroscopy as well as by mass spectrometry (ESI source) analysis. In particular, in the ^{13}C-NMR spectrum the signal corresponding to the quaternary carbon of the new linkage appeared at 158 ppm, a chemical shift fully consistent with a urea function.[11]

Eventually, organocatalyst **10** was achieved by palladium(0)-catalyzed removal of the Aloc group and subsequent *N*-dimethylation by reductive amination with formaldehyde and sodium cyanoborohydride (Scheme 2). The same sequence was successfully applied to glycosyl azides **3** and **5**, leading to glucosaminylurea-based organocatalysts **11** and **12** *via* **7** and **8**, respectively, while organocatalyst **13** was obtained by standard *O*-deacetylation of **10**. In contrast, *O*-methylated organocatalyst **14** was achieved from **4** in higher yield when *N*-dimethylation was performed before the formation of the ureido linkage.

Finally, we investigated a different route to obtain the (thio)ureido-linked organocatalyst. The silylated saccharide scaffold **3** was converted into glycosyl azide **15** by deprotection of the 2-amino group and *N*-dimethylation in 57% yield over two steps. Next, catalytic hydrogenation of the anomeric azide onto **15** was performed in the presence of the aryl isothiocyanate to afford glucosaminylthiourea organocatalyst **16** (Scheme 3).

Partial epimerization of the transient anomeric amine, however, occurred during the hydrogenation step, and organocatalyst **16** was obtained as an α,β mixture, evidenced by NMR analysis.[12]

In the next stage of our endeavor, the catalytic properties of the bifunctional organocatalyst were tested in the stereoselective addition of activated nucleophiles to nitroolefins.[13]

The catalytic activity of compounds **10–14** and **16** was first evaluated in the model reaction between *trans* β-nitrostyrene **17** and acetylacetone (Scheme 4); the reaction was typically performed in the presence of 10 mol% of catalyst for 18 h in dichloromethane at room temperature; the results obtained with chiral bifunctional catalysts of type **B** are reported in Table 1.

The poly-acetylated compound **10** was able to promote the reaction in modest yield and stereoselectivity. Derivatives bearing less sterically demanding hydroxyl groups were shown to catalyze the acetylacetone addition with improved efficiency; better yields were obtained with catalysts **14** and **13**, although with low enantioselectivity. The possibility that coordinating hydroxyl groups may interfere with the action of the bifunctional catalyst that should activate the reactive substrates by realizing a hydrogen

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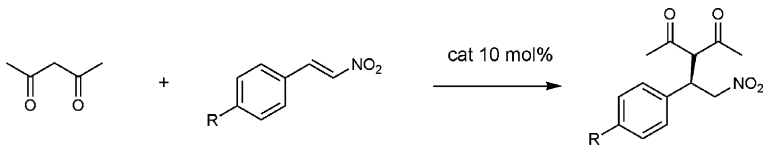

R = H	**17**	R = H	**18**
R = Me	**19**	R = Me	**20**
R = OMe	**21**	R = OMe	**22**
R = Cl	**23**	R = Cl	**24**
R = CF_3	**25**	R = CF_3	**26**

Scheme 4 Addition of acetylacetone to β-nitrostyrenes.

Table 1 The stereoselective addition of acetylacetone to β-nitrostyrene **17** at RT in DCM[a]

Entry	Catalyst	Yield%[b]	ee%[c]
1	**10**	35	28
2	**14**	40	50
3	**13**	57	20
4	**11**	25	**89**
5	**16**	27	55
6	**12**	36	40
7[d]	**11**	21	57
8[e]	**13**	83	45
9[e]	**11**	70	45

[a] Typical experimental conditions: 0.1 mol equiv. of catalyst, 1 mol equiv. of β-nitrostyrene, 1 mol equiv. of acetylacetone, 18 h reaction time in DCM at 25 °C. [b] Yields of isolated products. [c] As determined by HPLC on a chiral stationary phase; yields and ee are the average of duplicate experiments. [d] Reaction was run in the presence of 0.1 mol equiv. of acetic acid. [e] Reaction was run without solvent.

Table 2 Optimization studies for the organocatalytic addition of acetylacetone to β-nitrostyrene **17**[a]

Entry	Catalyst	Solvent	Yield%[b]	ee%[c]
1	**10**	Et_2O	27	18
2	**11**	DCM	25	**89**
3	**11**	Et_2O	21	59
4	**11**	Toluene	23	79
5[d]	**11**	neat	30	51
6[d]	**11**	DCM	n.d.	—
7[e]	**11**	DCM	27	71
8[f]	**11**	DCM	25	57
9[g]	**11**	DCM	**93**	**83**

[a] Typical experimental conditions: 0.1 mol equiv. of catalyst, 1 mol equiv. of β-nitrostyrene, 1 mol equiv. of acetylacetone, 18 h reaction time in DCM at 25 °C. [b] Yields of isolated products. [c] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments. [d] Reaction was run at 0 °C. [e] Reaction was run with 30% mol amount of catalyst. [f] Reaction was run with 10 mol equiv. of acetylacetone for 1 mol equiv. of nitrostyrene. [g] Reaction was run with 5 mol equiv. of nitrostyrene for 1 mol equiv. of acetylacetone.

Table 3 The addition of acetylacetone to β-nitrostyrenes catalyzed by **11**[a]

Entry	*R*	Product	Yield%[b]	ee%[c]
1	H	**18**	93	83
2	Me	**20**	71	82
3	OMe	**22**	67	55
4	Cl	**24**	84	84
5	CF_3	**26**	78	85

[a] Typical experimental conditions: 0.1 mol equiv. of catalyst, 5 mol equiv. of β-nitrostyrene, 1 mol equiv. of acetylacetone, 18 h reaction time in DCM at 25 °C. [b] Yields of isolated products. [c] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.

bond network, was considered responsible for the disappointing results. Indeed, the use of sugar-derived compounds with non-coordinating protecting groups at the hydroxy residues, such as silyl ethers afforded better results. Catalyst **11** promoted the reaction in 89% ee, a level of stereoselection comparable to that obtained with the Takemoto catalyst; in this case the urea derivative was shown to behave better than the corresponding thiourea-based catalyst **16**.[14] Unfortunately, also in this case, the addition product was isolated in low chemical yield. In the attempt to further improve the methodology the reaction was performed without solvent, in the presence of a large excess of acetylacetone. As expected, the product was obtained in higher yields, both with persilylated catalyst **11** and catalyst **13** and the same level of stereoselectivity (45% ee). A more polar reaction medium (such as acetylacetone) compared to dichloromethane negatively affected the coordination action of the catalyst towards the nitrostyrene.

By looking for the best experimental conditions, the catalytic behavior of the catalyst of choice **11** was investigated in different solvents (Table 2). Dichloromethane and toluene proved to be the solvents of choice; lower stereoselectivities were observed in more polar solvents like diethyl ether or by running the reaction in acetylacetone as solvent, even when the reaction temperature was lowered.

Unfortunately, the chemical yield was not improved either by increasing the catalyst loading up to 30% (entry 7, Table 2) or by performing the reaction with a great excess of acetylacetone in DCM (entry 8, Table 2); in this case the product was isolated with an even lower enantioselectivity (57% ee *vs.* 89% ee, entry 2 Table 2). However, the chemical yield was successfully improved by employing a five equivalent excess of nitrostyrene (see below for the discussion of this result); by running the reaction at 25 °C for 18 h the product was obtained in 93% yield and with only marginally decreased enantioselectivity (83% ee, entry 9, Table 2).

The general applicability of the catalyst of choice, **11**, was then briefly investigated. Differently substituted nitrostyrene derivatives were prepared and tested in the organocatalyzed reaction with acetylacetone (Table 3).

Catalyst **11** promoted the addition to the differently substituted nitroolefins in comparable chemical yields; generally, substrates bearing electron withdrawing substituents, such as halogens or a trifluoromethyl group, gave higher enantioselectivities than those

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with nitroolefins bearing electron donating groups (see entries 4–5 of Table 3 in comparison with entry 3).

At this stage it is very difficult to propose any hypothesis of rationalization of the stereochemical course of the reaction, also in view of the fact that the present multifunctionalized catalysts probably present more than one possible mechanism of action. These compounds are thought to operate as bifunctional catalysts; for example for the addition of acetylacetone to *trans* β-nitrostyrene it is quite reasonable to postulate a transition state depicted in Fig. 2. The nitrostyrene activation through double hydrogen bond coordination with the urea group and deprotonation of the 1,3-diketone by the basic amino group of the 1,2-diaminocylohexane moiety should keep the two reagents close enough to allow the catalyst to control the absolute stereochemistry of the process.

Working on this hypothesis, we performed some preliminary calculations with MM as well as with semiempirical methods, and were able to underline some critical features for the reaction promoted by sugar-derived catalysts.

A complete conformational analysis[15] of catalysts **10** and **11**, performed with an MMFFS force field, as included in the MacroModel package,[16] revealed the reason for the scarce stereoselectivity of the reaction promoted by catalyst **6**: in fact, not only the basic dimethylamino group, but also the three acetyl moieties can act as Lewis bases in this case.

With the acetylacetone enolate binding in four different positions, and thus four different relative orientations of the reactants being accessible, a significant lack of facial stereoselectivity is predicted, in agreement with the experimental data (Tables 1 and 2). On the other hand, oxygen atoms protected as silyl ethers are not basic, thus other catalysts such as **11**, **12** and **16** are much more stereoselective.

To further investigate the origin of the reaction stereoselectivity, theoretical calculations were performed on the two adducts between catalyst **11**, *trans* β-nitrostyrene and acetylacetone enolate, leading to the (*R*) and (*S*) products. Due to the size of the problem, the semiempirical AM1 Hamiltonian was selected.[17] In an exploratory study performed on the Takemoto catalyst (Fig. 1), we observed a significant correspondence between the energy difference of the two diastereoisomeric ternary adducts and the final enantioselection in the addition of ethyl malonate to *trans* β-nitrostyrene. In the case of the sugar-derived catalyst **11**, two structures **A** and **B** were fully optimized, and characterized as minima, for the adducts leading to products (*R*) and (*S*), respectively (Fig. 3).[18]

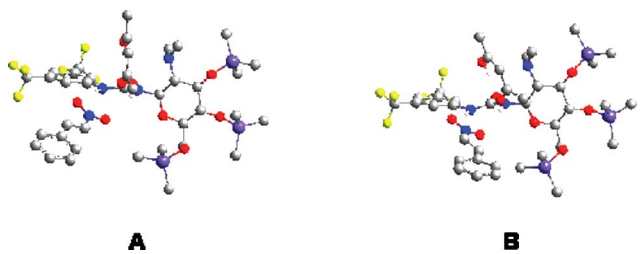

Fig. 3 AM1 structures **A** and **B** for the ternary complexes leading to the (*R*) and (*S*) adducts, respectively.

The origin of the stereoselection seems to depend upon the steric hindrance due to the silylated protecting groups of the carbohydrate oxygens; the small energy difference between complexes **A** and **B** (0.03 kcal mol^{-1}) increases to 2.9 kcal mol^{-1} when the complexes of (*R*) and (*S*)-**18** with catalyst **11** are considered (structures **A′** and **B′** in Fig. 4), favoring the (*R*) product. Another feature of the reaction is revealed by these calculations: the complexes between reaction product (*R*) or (*S*)-**18** and catalyst **11** are extremely stable; in particular, decomplexation of **A′** to give (*R*)-**18** and catalyst **11** requires about 8 kcal mol^{-1}. For this reason, probably, an excess of *trans* β-nitrostyrene is recommended to obtain a reasonable reaction yield, in accordance with the experimental findings in Table 2.

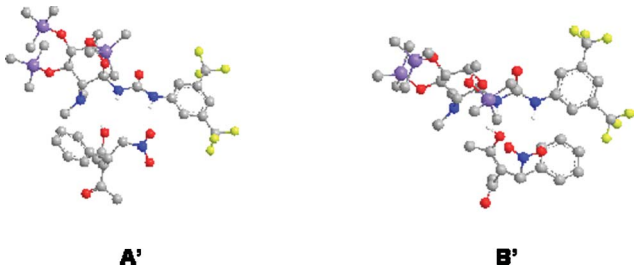

Fig. 4 AM1 structures **A′** and **B′** for the complexes of (*R*) and (*S*)-**18** with catalyst **11**, respectively.

In order to further explore the catalytic behavior of this novel class of catalysts in more challenging transformations, the addition of activated nucleophiles to imines was studied; in particular, we focused our attention on reactions of imines with 1,3-dicarboxylic esters.

The addition of diethyl malonate to the *N*-Boc imine of benzaldehyde was investigated; the reaction was typically performed in dichloromethane at room temperature for 12 h in the presence of 10 mol% of catalyst to afford the corresponding Mannich product **27**, that was isolated by flash chromatography; the results are reported in Scheme 5.

Once again, compounds bearing hydroxyl groups able to act as hydrogen bonding acceptors, like catalyst **14**, promoted the reaction with low enantioselectivity, although in good chemical yield. In contrast, molecules bearing more sterically demanding hydroxyl protecting groups catalyzed the addition to Boc-imines in lower yields. However, for this transformation the silyl ether was shown to be the protecting group of choice, in order to guarantee good levels of stereoselection. With catalysts **16** and **12** the product was isolated with good enantioselectivity with 75% and 77% ee, respectively, but it was with catalyst **11** that the best results were observed: the expected β-amino ester was obtained in 81% enantioselectivity after an 18 h reaction at room temperature.

In conclusion, the synthesis of a new family of chiral bifunctional organocatalysts was successfully realized, starting from a readily available, cheap, enantiomerically pure material such as D-glucosamine. For the first time, the saccharide unit was employed as a chiral scaffold alternative to 1,2-*trans*-diaminocyclohexane, bearing two catalytic residues located in a well defined spatial arrangement. The activity of the novel catalysts was investigated in a model reaction: the addition of acetylacetone to nitrostyrene; in the best conditions, enantioselectivities up to 89% were obtained. The same metal-free catalysts were then employed in the addition of activated nucleophiles to imines: in the reaction of diethyl malonate with *N*-Boc imines and the products were isolated in up to 81% ee. An attempt to rationalize the stereochemical outcome

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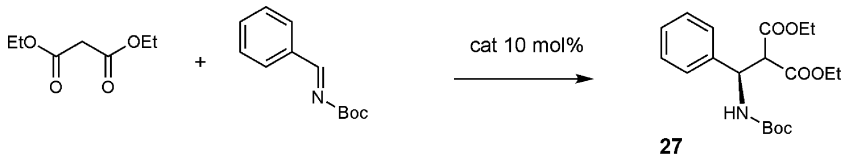

cat. **16**	23% yield, 75% e.e.
cat **11**	25% yield, **81% e.e.**
cat **14**	55% yield, 11% e.e.
cat **12**	21% yield, 77% e.e.

Scheme 5 The addition of diethyl malonate to *N*-Boc imines.

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of the reaction and the behaviour of the novel catalysts was also proposed on the basis of preliminary semiempirical (AM1) studies. We believe that these results represent only the first step towards the development of new carbohydrate-based metal-free catalytic systems, which may offer several attractive features, like ready availability, low cost, polyfunctionalization, the presence of several well defined stereocenters and the possibility of different facile modifications for the fine tuning of their catalytic properties.

Experimental Section

Computational

All MMFFS calculations were run with the MacroModel package; conformational analyses were performed with the stochastic MCMM method, with all exocyclic dihedral angles set as variables; convergence was considered achieved when all structures within 3 kcal mol^{-1} from the global minimum were sampled several times. AM1 calculations were run with the Gaussian03 package.[19] All located structures were characterized as minima by means of a full vibrational analysis.

General

All reactions were carried out in oven-dried glassware with magnetic stirring under a nitrogen atmosphere, unless otherwise stated. All commercially available reagents, including dry solvents, were used as received. Organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum using a rotatory evaporator. Nonvolatile materials were dried under high vacuum. Reactions were monitored by thin-layer chromatography on pre-coated Merck silica gel 60 F254 plates and visualized either by UV or by staining with a solution of cerium sulfate (1 g) and ammonium heptamolybdate tetrahydrate (27 g) in water (469 mL) and concentrated sulfuric acid (31 mL). Flash chromatography was performed on Fluka silica gel 60. Proton NMR spectra were recorded at 300 K (unless otherwise stated) on spectrometers operating at 300, 400 or 500 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). In ^{13}C NMR spectra, signals corresponding to aromatic carbons are omitted. Optical rotations were obtained on a polarimeter at 589 nm using a 5 mL cell with a length of 1 dm. HPLC for ee determination was performed under the conditions reported below. High resolution mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with Mass Spectrometer APEX II & Xmass software (Bruker Daltonics). Mass spectra (MS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source.

2-*N*-allyloxycarbonyl-2-amino-2-deoxy-β-D-glucopyranosyl azide (2)

Compound **1** (1.95 g, 4.7 mmol)[6] was dissolved in dry methanol under an inert atmosphere and a 1 M soln of MeONa in MeOH was added at rt until basic pH was reached. After the disappearance of the starting material (TLC analysis), the reaction was quenched with IR-120 resin (H^+ form), filtered and concentrated under reduced pressure, obtaining compound **2** as a yellow glass (1.35 g, qu). The complete removal of the acetyl groups was ascertained by NMR analysis and the compound was used in the following steps without further characterization.

2-*N*-allyloxycarbonyl-2-amino-2-deoxy-3,4,6-tri-*O*-triethylsilyl-β-D-glucopyranosyl azide (3)

Compound **2** (705 mg, 2.45 mmol) was dissolved in dry DMF under an inert atmosphere and cooled to –20 °C. *Sym*-collidine (3.89 mL, 29.4 mmol) and TESOTf (3.05 mL, 3.47 mmol) were slowly dropped into the solution. After 24 h the reaction was quenched by pouring it into $NaHCO_3$ saturated soln and extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent Hex/AcOEt 9 : 1) providing compound **3** (1.50 g, 97%) as a glassy solid.

α_D = –32.15° (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.88–6.00 (m, 1H, CH_{vin}), 5.55 (d, 1H, J_{NH-2} = 9.4 Hz, NH), 5.37–5.205 (m, 2H, $CH_{2\,vin}$), 4.98 (d, 1H, J_{1-2} = 4.8 Hz, H-1), 4.61–4.58 (m, 2H, $CH_{2\,all}$), 4.15 (bt, 1H, J_{1-2} = 9.5 Hz, H-6a), 3.91 (t, 1H, J = 3.8 Hz, H-4), 3.88–3.79 (m, 2H, H-6b, H-3), 3.74–3.69 (m, 1H, H-5), 3.63-3.58 (m, 1H, H-2), 1.03–0.92 (m, 27H, $CH_{3\,TES}$), 0.73–0.50 (m, 18H, $CH_{2\,TES}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 117.5, 88.0, 80.1, 72.7, 69.3, 65.7, 62.5, 54.5, 6.8, 4.7. ESI-MS 654.2 g mol^{-1}

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(+Na). Anal. calcd for $C_{28}H_{58}N_4O_6Si_3$ (631.04): C, 47.27; H, 6.71; N, 16.96%; Found: C, 47.31; H, 6.68; N, 17.00%.

Synthesis of glucosaminyl ureas – general procedure

The glucosyl azide (1 mmol) and triphenylphosphine (1.1 mmol) were dissolved in dry THF under a nitrogen atmosphere and stirred overnight at rt. 3,5-Bis-trifluorometilphenyl isothiocianate (1 mmol) was added and the reaction was stirred for a further 3 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography, obtaining the pure urea derivative.

N-[*N*-allyloxycarbonyl-2-amino-2-deoxy-3,4,6-tri-*O*-triethylsilyl-β-D-glucopyranosyl], *N*′-(3,5-bis-trifluoromethyl)phenyl urea (7)

Chromatographic purification of urea **7** was performed using Hex/EtOAc 95 : 5 + 1% TEA as eluent (yield 60%).

α_D = −3,69° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H, Ar), 7.74 (s, 1H, Ar), 7.49 (bd, 1H, NH), 6.36 (bs, 1H, NH), 5.96–5.88 (m, 1H, H_{vin}), 5.65 (bs, 1H, NH), 5.36–5.23 (m, 2H, $CH_{2\,vin}$), 4.68–4.56 (m, 3H, $CH_{2\,all}$, H-6a), 4.38 (bs, 1H, H-6b), 4.08 (bt, 1H, H-1), 3.95–3.83 (m, 2H, H-2, H-3), 3.57 (bs, 1H, H-5), 3.44 (d, 1H, *J* = 2.7 Hz, H-4), 1.06–0.95 and 0.83 (m, 27H, $CH_{3\,TES}$), 0.72–0.63 (m, 18H, $CH_{2\,TES}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.2, 117.8, 81.8, 71.0, 68.8, 68.4, 66.3, 58.7, 52.3, 6.7, 6.4, 4.5, 4.0; ESI-MS 883.5 g mol^{-1} (+Na); Anal. calcd for $C_{37}H_{63}F_6N_3O_7Si_3$ (860.16): C, 51.66; H, 7.38; N, 4.89%; Found: C, 51.69; H, 7.35; N, 4.80%.

Removal of the Aloc group and *N*,*N*-dimethylation – general procedure

The starting urea (1 eq.) was dissolved in dry dichloromethane, then $Pd(PPh_3)_4$ (0.02 eq.), AcOH (2.4 eq.) and Bu_3SnH (1.1 eq.) were sequentially added to the solution. After 30 min the solvent was removed under reduced pressure, the residue was dissolved in THF and paraformaldehyde aq. 37% solution (35 eq.) and $NaCNBH_3$ (8 eq.) were added. The reaction was stirred at rt for 2 h, then AcOH was added until pH 4–5. After stirring for a further 3 h, the reaction mixture was cooled to 0 °C and aq. NaOH 5% was added until basic pH was reached. The mixture was extracted with EtOAc, the combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography, obtaining pure bifunctional organocatalyst.

N-[2-*N*,*N*-dimethylamino-2-deoxy-3,4,6-tri-*O*-triethylsilyl-β-D-glucopyranosyl], *N*′-(3,5-bis-trifluoromethyl)phenyl urea (11)

Chromatographic purification of urea **11** was performed using Hex/EtOAc 98 : 2 + TEA 1% as eluent (yield 47%).

α_D = −2.8° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (bs, 1H, NH), 7.58 (s, 2H, Ar), 7.28 (bs, 1H, Ar), 6.42 (d, 1H, *J* = 10.3 Hz, NH), 5.62 (t, 1H, *J* = 10.2 Hz, H-1), 3.93 (dd, 1H, *J* = 2.8, 10.6 Hz, H-6a), 3.84–3.78 (m, 2H, H-3, H-5), 3.66 (t, 1H, *J* = 9.6 Hz, H-6b), 3.41 (bt, 1H, H-4), 2.49–2.45 (m, 7H, H-2, NMe_2), 1.70–0.99 (m, 18H, 6 $CH_{3\,TES}$), 0.82 (t, 9H, *J* = 7.9 Hz, 3 $CH_{3\,TES}$), 0.76–0.66 (m, 12H, 6 $CH_{2\,TES}$), 0.41 (q, 6H, *J* = 7.9 Hz, 3 $CH_{2\,TES}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.8, 80.7, 78.2, 75.2, 74.0, 70.6, 64.7, 41.9, 7.2, 6.9, 6.4, 5.3, 5.2, 3.9; ESI-MS 804.3 g mol^{-1}; Anal. calcd for $C_{35}H_{63}F_6N_3O_5Si_3$ (804.14): C, 52.28; H, 7.90; N, 5.23%; Found: C, 52.34; H, 7.85; N, 5.31%.

General procedure for the Michael addition reaction of 2,4-pentanedione with *trans*-β-Nitrostyrene

Bifunctional catalyst (0.02 mmol, 0.1 eq.) and *trans*-β-nitrostyrene (30 mg, 0.20 mmol, 1 eq. or 1 mmol, 5 eq., see text) were charged in a 10 mL round bottom flask under nitrogen. DCM (0.5 mL) was added and, after 5 min stirring at 23 °C, 2,4-pentanedione (0.023 mL, 0.22 mmol, 1.1 eq.) was added *via* syringe. The reaction was stirred at 23 °C for 18 h, then the solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography on silica gel (1 × 16 cm silica, petroleum ether : AcOEt 7 : 3, R_f 0.25) to afford pure 3-((*R*)-2-nitro-1-phenylethyl)pentane-2,4-dione.

^{1}H-NMR (300 MHz, CDCl3): δ 7.35–7.1 (m, 5H), 4.65–4.55 (m, 2H), 4.3 (d, *J* = 10.9 Hz, 1H), 4.2 (m, 1H), 2.3 (s, 3H), 1.9 (s, 3H). HPLC (Daicel Chiralpak AD, hexane : *i*-propanol 80 : 20, flow rate = 1 mL min^{-1}, *P* = 21 bar, λ = 210 nm): t_{minor} = 8.69 min, t_{major} = 11.14 min. $[\alpha]_D^{20}$ = −13.98° (*c* = 0.1, $CHCl_3$).

General procedure for the Mannich reaction of diethyl malonate with imines

Bifunctional catalyst (0.019 mmol, 0.1 eq.) and Boc-imine (0.19 mmol, 1 eq.) were charged in a 10 mL round bottom flask under nitrogen. DCM (0.5 mL) was added and, after 5 min stirring at the indicated temperature, diethyl malonate (0.058 mL, 0.38 mmol, 2 eq.) was added *via* syringe. The reaction was stirred at 25 °C for 18 h, then the solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography on silica gel. (1 × 16 cm silica, petroleum ether : AcOEt 7 : 3, R_f 0.25)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.3 (m, 5H), 6.25 (brs, 1H), 5.4 (brs, 1H), 4.35–4.25 (m, 4H), 4.1 (d, 1H), 3.7 (s, 3H), 1.5 (t, 3H), 1.25 (t, 9H), 1.15 (t, 3H). $[\alpha]_D^{20}$ = −5.7° (*c* = 0.1, $CHCl_3$) (*R*) enantiomer.

HPLC (Daicel Chiralpak AD, hexane : *i*-propanol 90 : 10, flow rate = 0.8 mL min^{-1}, *P* = 15 bar, λ = 225 nm) t_{major} = 18.63 min, t_{minor} = 23.36 min.

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11 A reasonable explanation for this result is that the initially-formed triphenyl phosphinimine **A** is transformed into the carbodiimide **B** *via* an aza Wittig-type reaction with the arylisothiocyanate. The subsequent aqueous work-up delivered the glycosyl urea **6**.

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