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New glycosyl-α-aminotetrazole-based catalysts for highly enantioselective aldol reactions

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ABSTRACT

Direct aldol reactions of acetone with aromatic aldehydes have been achieved in high yielding and enantioselective processes using glycosyl-α-aminotetrazoles as a new class of organocatalysts. Computational studies at DFT level have been performed to account for the experimental observations.

1. Introduction

Amino acid organocatalysis have recently received much attention since the discovery[1,2] that L-proline is able to catalyze direct intermolecular aldol or Mannich reactions. Although these transformations are highly enantioselective, they all rely on fairly polar solvents, such as DMSO, due to the insoluble nature of L-proline itself, as well as on large amounts of L-proline to achieve reasonable yields. Consequently, small synthetic organic molecules with greater solubility in conventional solvents would be highly desirable as an alternative to L-proline. Based on these grounds, most investigations have focused on L-proline derivatives, such as aminotetrazole catalysts. This is the case of (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole **I**[3a,b] (Fig. 1) that has promoted remarkable selectivity compared to L-proline in organocatalytic Mannich[4] reactions, alanine-tetrazole **II**,[5] and cyclopentylamine-tetrazole **III** (Fig. 1).[6a,b] However, no glycosyl substituted tetrazole has been described as a catalytic system in related synthetic transformations, and this is very surprising, because carbohydrates have been largely used as chiral ligands in the search for high catalytic activities and enantioselectivities.[7] Recently, carbohydrates have been used as auxiliary agents to anchor acyclic diamines derived from α-amino acids in organocatalytic addition of acetylacetone to *trans*-β-nitrostyrene.[8a–d] Organocatalysts derived from the combination of carbohydrates and cinchona alkaloid have also been used in asymmetric synthesis of tertiary α-hydroxy phosphonates.[8e] L-proline attached to carbohydrate (catalyst **IV**) also demonstrated that the hydroxyl group presumably promotes the coordination leading to aldol derivatives in good yields and moderate enantioselectivity.[9] Glycosyl-β-amino acids **V**[10] and D-glucosamine derivatives **VI**[11] have also been studied in catalytic asymmetric aldol reactions.

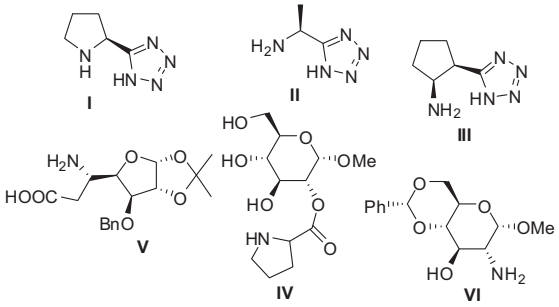

Fig. 1. Organocatalysts.

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With these precedents in mind, we report here that the new glycosyl-α-aminotetrazoles (**1d**, **2d**, and **3b**) (Fig. 2) promote high yielding and enantioselective direct asymmetric aldol reactions of different aromatic aldehydes with acetone.

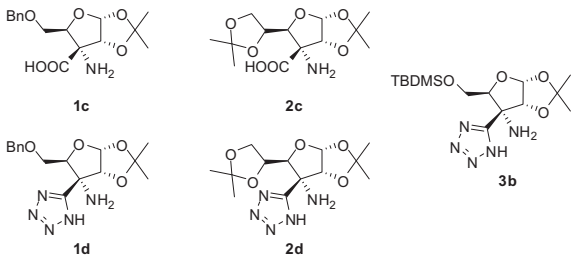
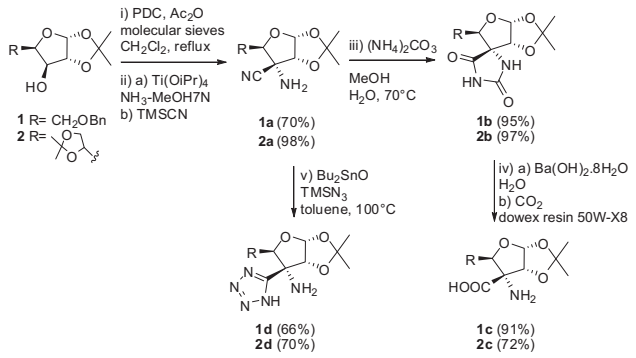


Fig. 2. The synthesized catalysts.

2. Results and discussion

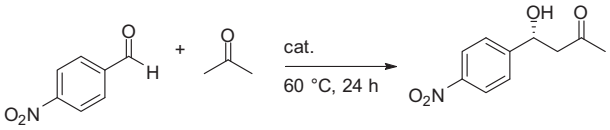
In the first exploratory experiments we tested our recently reported GlycoAminoAcids (GAAs)[12] **1c** and **2c** (Fig. 2), readily prepared from precursors **1**[13] and commercially available **2** (Scheme 1). Oxidation using PDC afforded crude uloses, which were submitted to our modified Strecker reaction leading stereoselectively to α-aminonitriles **1a**[14] and **2a**[15] in 70% and 98% yields, respectively. A Bücherer–Bergs reaction led almost quantitatively to the spiranic hydantoïns **1b** and **2b**. Finally, GAAs **1c** and **2c** were obtained by ring opening using barium oxide, whereas the bioisostere tetrazole derivatives **1d** and **2d** were synthesized from **1a** and **2a** using $TMSN_3/Bu_2SnO$ in toluene at 100 °C in 66% and 70% yields, respectively (Fig. 2).



Scheme 1.

With these compounds in hands, first, we carried out the reaction of 4-nitrobenzaldehyde with acetone, catalyzed by GAAs **1c** and **2c** (20 mol %), under different experimental conditions.[16] At room temperature no reaction was observed, but after heating at 60 °C, (*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one was obtained in only 19% and 3% yields (entries 1 and 2, Table 1). Next, and view of these results we used tetrazoles **1d** and **2d** (Fig. 2). To our delight, and under the same experimental conditions, the aldol was isolated in 36% and 89% yields, respectively (entries 3 and 4) showing ees>>88%. A reduction on the amount of the catalyst used (entries 5 and 6) afforded the aldol derivative in a similar range of yields (87–89%) and ee (82–87%), except when the catalyst was loaded at 5 mol %, the aldolisation requiring then longer reaction times (48 h).

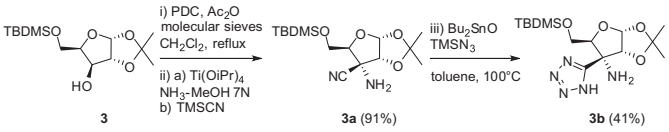
Table 1
Direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by chiral amino acids (**1c**, **2c**) and aminotetrazoles (**1d**, **2d**)[a]



Entry	Catalyst (mol %)	Yield[a] (%)	ee (%)[b]
1	**1c** (20)	19	14 (*R*)
2	**2c** (20)	3	nd[d]
3	**1d** (20)	36	95 (*R*)
4	**2d** (20)	89	88 (*R*)
5	**2d** (5)[c]	87	82 (*R*)
6	**2d** (10)	89	87 (*R*)
7	**3b** (10)	98	81 (*R*)

[a] Yield of product isolated by column chromatography.
[b] The ee value of the product was determined by HPLC analysis using a chiral column (chiralpak AS-H, Daicel Chemical Industries).
[c] The absolute configuration was determined by comparison of the HPLC retention time of the product with reported data.[17] 48 h of reaction time.
[d] nd: not determined.

In order to clearly understand the role of the carbohydrate moiety, we synthesized catalyst **3b** in a similar way, but starting from 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose **3**,[18] in 41% yield from **3a** (Scheme 2).



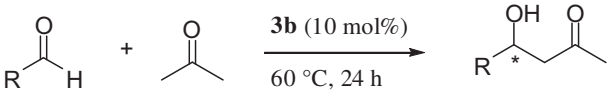
Scheme 2.

Screening the reaction of 4-nitrobenzaldehyde with acetone using catalyst **3b** (entry 7, Table 1), the aldol product was nicely obtained in an almost quantitative yield (98%) and 81% ee.

Having established the critical effect on both enantioselectivity and yield, by changing the carboxylic group to tetrazole, we next investigated the potent and readily available catalyst **3b** in the aldol reaction of differently substituted benzaldehydes with acetone, in order to test the scope and generality of the reaction.

As shown in Table 2, different types of substituted aromatic aldehydes were found suitable reaction substrates, the corresponding aldol adducts being isolated in good yields and high

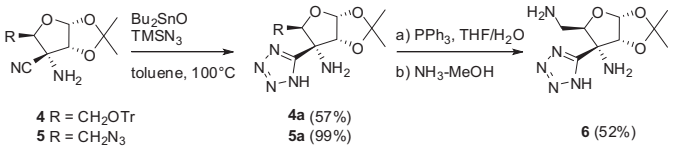
Table 2
Direct asymmetric aldol reaction of aldehyde with acetone catalyzed by chiral aminotetrazole (**3b**)



Entry	R	Yield[a] (%)	ee (%)[b]
1	3-ClC_6H_4	34	98 (*R*)
2	2-Naphtyl	46	77 (*R*)
3	2-Cl–6-FC_6H_3	99	92 (*S*)
4	3-FC_6H_4	73	96 (*R*)
5	2,5-$F_2C_6H_3$	86	75 (*R*)
6	4-$NO_2C_6H_4$	98	81 (*R*)
7	4-CNC_6H_4	99	83 (*R*)

[a] Yield of product isolated by column chromatography.
[b] The ee value of the product was determined by HPLC analysis using a chiral column (chiralpak AS-H, AD-H Daicel Chemical Industries). The absolute configuration was determined by comparison of the HPLC retention time of the product with reported data.[17]

enantioselectivities. One intriguing result is the fact that the *S*-isomer (entry 3) was obtained while the other substrates afforded *R*-isomer. In order to rationalize the substrate's influence and sugar skeleton on the asymmetric induction, aminotetrazole catalyst with modified substituent at C-5 were examined (Scheme 3).



Scheme 3.

Catalysts **4a** and **5a** were obtained in 57% and 99% yield, respectively from **4**[13] and **5**. Reduction of **5a** with triphenylphosphine led to the diamino-tetrazole **6** in 52% yield. Those catalysts were also submitted to the aldol reaction and the results are summarized in Table 3.

tetrazole ring can exist in two different tautomers (2*H* and 3*H*). The calculations indicate that 2-tautomer is more stable than the 3-tautomer form by 1.6 and 1.9 kcal/mol for the *anti* and *syn*-enamine of **3b**, respectively. Similar conclusions on the higher stability of the 2-tautomer have been reported by Domingo et al.[20] Moreover, because the transition structures that involve intramolecular proton catalysis would be the more energetically viable, we discard 3*H*-tautomer as operative intermediate.[21]

At this point, we have analyzed the transition states that allow for intramolecular acid catalysis from the tetrazole proton of the 2-tautomer to the aldehyde acceptor. For each enamine, *anti* and *syn*, at least four possible transition structures can be envisaged depending of the incoming benzaldehyde: two transition structures depending on the attack face of the aldehyde (*Re*- or *Si*-face), and two more depending on the dihedral angle between the unsaturated reactive groups, alkene of enamine and carbonyl group of the aldehyde (+60° and −60°, Fig. 4).

In order to get insights into the origin of the striking enantioselectivity found for the asymmetric aldol reaction of 4-nitrobenzaldehyde catalyzed by **3b**, firstly, we have calculated the

Table 3
Influence of C-5 substituent

Entry	Ar	**4a**		**2d**		**5a**		**6**		**1d**	
		Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)
1	3-ClC_6H_4	32	81 (*R*)	90	67 (*R*)	53	96 (*R*)	47	98 (*R*)	64	91 (*R*)
2	2-Naphtyl	15	69 (*R*)	38	84 (*R*)	53	82 (*R*)	nd[a]	nd[a]	27	91 (*R*)
3	2-Cl−6-FC_6H_3	44	89 (*S*)	55	97 (*S*)	99	96 (*S*)	25	14 (*S*)	45	98 (*S*)
4	3-FC_6H_4	32	92 (*R*)	54	95 (*R*)	54	96 (*R*)	35	97 (*R*)	<10	nd[a]
5	2,5-$F_2C_6H_3$	99	80 (*R*)	88	75 (*R*)	92	80 (*R*)	30	<1 (*R*)	76	90 (*R*)
6	4-$NO_2C_6H_4$	97	91 (*R*)	89	87 (*R*)	91	88 (*R*)	18	9 (*R*)	36	95 (*R*)[b]
7	4-CNC_6H_4	70	88 (*R*)	90	91 (*R*)	82	88 (*R*)	34	6 (*R*)	42	90 (*R*)

[a] Not determined.
[b] Catalyst (20 mol %) was added.

As expected, all the catalysts gave similar results in ee% excepted for catalyst **6**, which afforded poor ee%. Substrate 2-Cl−6-FC_6H_3 favors in all cases *S*-isomer showing in this case that the aldol compound is not catalyst-dependent.

In order to rationalize these results including the observed asymmetric induction, we undertook a DFT study. The focus of our investigation was to determine why the *R*-isomer is favored in most cases, and for the most efficient catalyst **3b** in particular, and why this trend is not followed for substrate 2-Cl−6-FC_6H_3 whatever the catalyst. Initially, we have explored the possible transition structures for different aromatic aldehydes. Organocatalyzed aldol reaction is presumed to proceed via an enamine intermediate.[19] Therefore, the model system we have studied involves the reaction of the *anti* or *syn*-enamines of **3b** with acetone (Fig. 3). The *anti* and *syn* refer to orientation of the enamine with respect to the tetrazole.

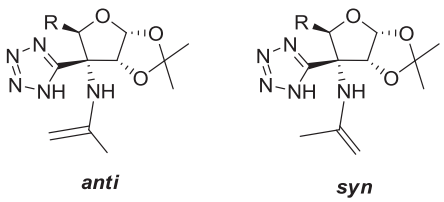


Fig. 3. Enamines of the tetrazole-based organocatalyst and acetone.

For **3b**, the conformer *anti* is 3.3 kcal/mol more stable than the rotamer *syn* because of unstabilizing steric interactions between the methyl group and R in the *syn*-enamine. On other hand, the plausible transition structures. Table 4 summarizes the relative free energies and main geometric parameters found. The data show that the transition structures showing additional H-bond between the carbonyl and the enamine were notably favored.[17a,22] Transition states, which lack this interaction are higher in energy by 6.8–9.5 kcal/mol. In addition, the preferred *Re*-face attack of the benzaldehyde poses the aryl group facing out. This minimizes the steric interaction between the aldehyde substituent and the methyl or substituents of the sugar ring of the enamine (Fig. 5), placing the substituent in a pseudoequatorial conformation.[23] Accordingly, this attack mode also shows a more perfect staggering of substituents around the forming C–C bond. Since this intermolecular step is exothermic, the earlier the transition state, the lower the energy barrier and the longer the distance of the forming C–C bond. Thus, the favored transition structure involves the attack of the *anti*-enamine on the *Re*-face of the aldehyde in an approaching angle of −60° and shows the longer forming C–C bond length while the tetrazole proton is only slightly transferred. This kinetically preferred structure drives to the *R*-enantiomer, in agreement with experiment.

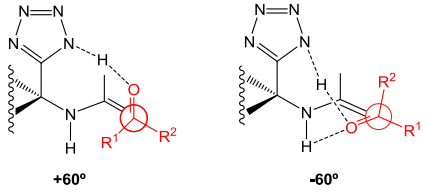


Fig. 4. Plausible transition structures depending on the carbonyl approaching angle.

Table 4
Relative free energies (kcal/mol) and main geometric parameters (Å) of the possible transition structures for the addition of 4-nitro and 2-chloro-6-fluorobenzaldehyde to enamine of **3b**

				4-Nitro				2-Cl, 6-F			
				$\Delta\Delta G^{\#}$	C–C	O–H	N–H	$\Delta\Delta G^{\#}$	C–C	O–H	N–H
anti	+60	*Si*	*S*	**6.8**	1.73	1.35	1.17	**2.8**	1.77	1.36	1.17
anti	+60	*Re*	*R*	**9.3**	1.72	1.33	1.17	**7.2**	1.74	1.32	1.19
anti	−60	*Si*	*S*	**1.8**	1.82	1.62	1.06	**0.0**	1.94	1.74	1.04
anti	−60	*Re*	*R*	**0.0**	1.88	1.61	1.06	**2.4**	1.89	1.59	1.07
syn	+60	*Re*	*R*	**9.2**	1.75	1.37	1.16	**5.7**	1.78	1.39	1.15
syn	+60	*Si*	*S*	**9.5**	1.80	1.52	1.10	**8.0**	1.89	1.63	1.11
syn	−60	*Re*	*R*	**7.7**	1.77	1.38	1.15	**7.6**	1.73	1.32	1.19
syn	−60	*Si*	*S*	**6.3**	1.81	1.46	1.11	**3.0**	1.83	1.46	1.11

The data computed for the possible transition structures for other differently substituted benzaldehydes catalyzed by **3b** show similar trends. In general, the transition structures showing the additional H-bond between the carbonyl and the enamine were notably favored (for instance, for 3-F and 3-Cl, see Fig. 6). For all the aldehydes but for 2-Cl–6-FC_6H_3, the transition structures involving the *anti*- are favored over the *syn*-enamine due to the lower distortion to accommodate the proton transfer from the tetrazole unit to the developing alkoxide, and also to the unfavorable steric interactions between the methyl moiety of the enamine with the C-5 moiety and the aryl group. Moreover, the attack on the *Si*-face of the aldehyde involves steric contacts that force change from the ideal staggered substituents to more eclipsed arrangements around the forming C–C bond. In contrast, the attack on the *Re*-face avoids steric interactions with the aryl moiety and leads to the kinetically favored enantiomer *R*, consistent with the experimental observations.

However, for substrate 2-Cl–6-FC_6H_3 we have observed that the *Si*-face attack on the *anti*-enamine is favored because of the electrostatic stabilizing interaction between the fluorine substituent of the aromatic ring and the proton of the methyl group of the enamine, as the F–H distance suggest (2.59 Å).[24] This effect is strong enough to revert the selectivity and favor the *Si*-face attack over the *Re*-face attack. Remarkably, the rotation of the aryl ring along the C–C(O) bond drives to a transition structure 5.8 kcal/mol higher in energy due to unfavorable steric interactions between the chlorine atom and the methyl group (Fig. 7). Finally, it should be noted that this 2,6-halo-substitution involves stronger electrostatic X–O repulsions in the *Re*-face attacking (F–O=2.76 Å and Cl–O=3.05 Å in the best cases $\mathbf{TS_{D-4}}$ and $\mathbf{TS_{D-4'}}$, respectively, vs 2.94 and 3.23 Å, for $\mathbf{TS_{D-3}}$ and $\mathbf{TS_{D-3'}}$, respectively, for the *Si*-face attack; see Fig. 7) because of the shorter C–C forming bond and higher pyramidalization of the carbonyl carbon. Therefore, the opposite

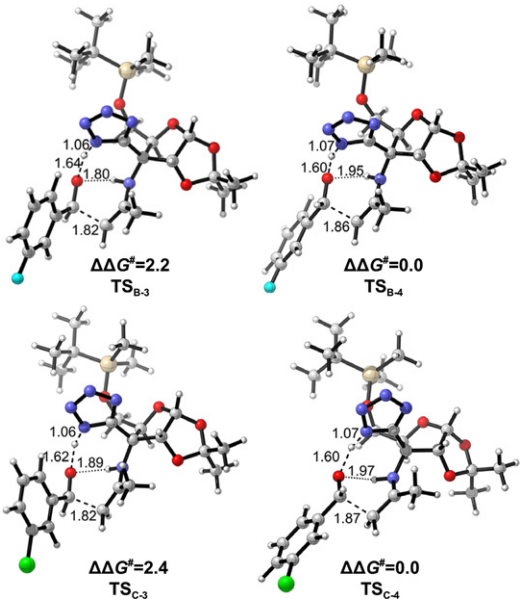


Fig. 6. Relative free energies (kcal/mol) of the most favorable transition structures leading to the enantiomers *R* (right) and *S* (left) for the addition of the enamine of **3b** to 3-fluoro- (top) and 3-chlorobenzaldehyde (bottom).

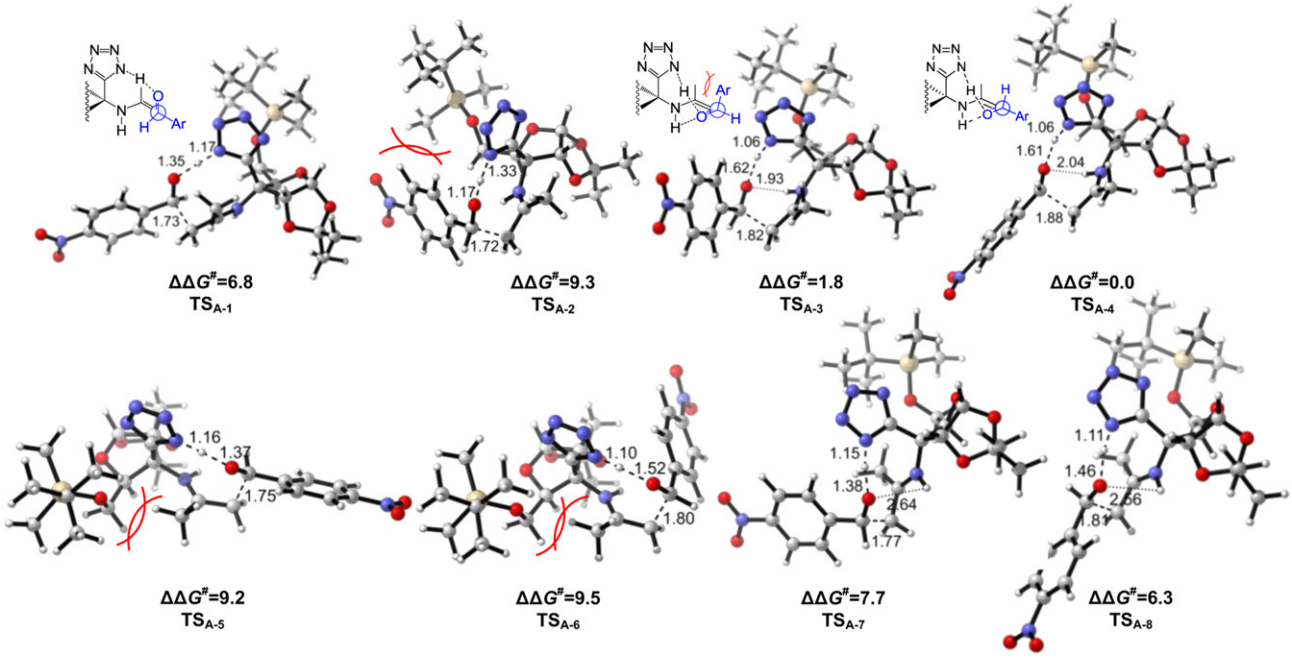


Fig. 5. Relative free energies (kcal/mol) of the possible transition structures for the addition of the *anti*- (top) and *syn*-enamine (bottom) of **3b** and 4-nitrobenzaldehyde. Some schematic Newman projections along the forming C–C bond have been depicted for clarity purpose.

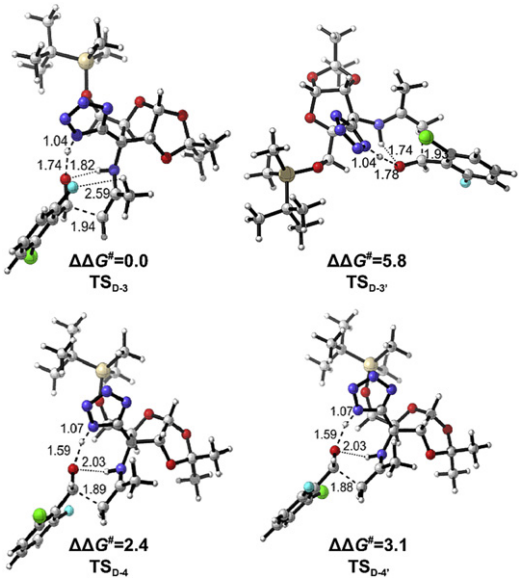


Fig. 7. Relative free energies (kcal/mol) of the most favorable transition structures for the attack of *anti*-enamine of **3b** to the *Si*-face (top) and *Re*-face attack (bottom) of 2-Cl–6-FC_6H_3. Plausible rotamers (right) are shown for comparison.

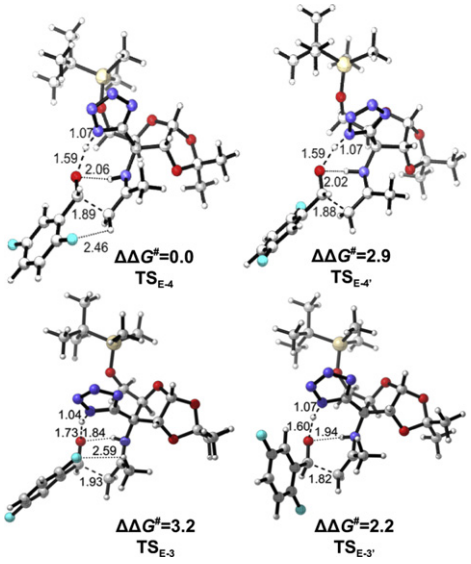


Fig. 8. Relative free energies (kcal/mol) of the most favorable transition structures for the attack of *anti*-enamine of **3b** to the *Re*-face (top) and *Si*-face attack (bottom) of 2,5-$F_2C_6H_3$. Plausible rotamers (right) are shown for comparison.

stereoselectivity for the acceptor 2-Cl–6-FC_6H_3 is probably due to the favorable weak H-bond,[25] and the less significant electrostatic X–O interactions for the *Si*-face attack.

For other catalysts, substrate 2-Cl–6-FC_6H_3 also favors *S*-isomer, probably because of analogous gauche interactions around the forming C–C bond.

According to these considerations, the aldolisation with the benzaldehyde 2,5-$F_2C_6H_3$ would afford the *S*-enantiomer by attacking of the *anti*-enamine on the *Si*-face. Nevertheless, calculations indicate once again that the *R*-enantiomer alcohol is favored over the *S*-isomer, in agreement with the experimental evidences. The energetically favored transition structure implies minimized unfavorable steric interactions with the enamine in a nearly perfect staggering around the forming C–C bond, as for other benzaldehydes related above (Figs. 5 and 6).

Moreover, we observed the formation, for the *Re*-face attack, of an H-bond between the alkene proton at the enamine and the fluorine atom (Fig. 8), shorter (2.46 Å) than the H-bond with the alkane for the *Si*-face attack (2.59 Å), and hence probably stronger, due to the higher acidity of the alkene proton. Contrarily to the 2,6-dihalosubstituted aldehyde, the free rotation around the C–C(O) bond connecting the aldehyde and aryl groups avoids unfavorable electrostatic F–O contacts, thus restoring the *Re*-face attack preference. These observations can account for the computed relative free energy values of the transition structures, 2.2 kcal/mol lower for the *Re*-face attack, which agrees with the experimental data.

An important aspect of this model is that the transition state is stabilized through hydrogen bondings and involves a proton transfer. Therefore, a small change in the p*K*a value of an organic compound would affect its catalytic activity and selectivity in the aldol reactions.[23b,26] In addition, although tetrazoles and carboxylic acids have similar p*K*a values, the tetrazole group is much more lipophilic and does not suffer from solvation issues in organic solvents. Thus, we performed calculations on the differences between catalysts **1c** and **1d**, which provides yields of 19 and 64%, respectively, for substrate 3-Cl, and ee% of 14 (*R*-) and 91 (*R*-). The computed results reveal a free energy of activation 1.6 kcal/mol higher for **1c** than for its isostere **1d**. The most stable transition structure for the formation of the *R*-enantiomer is only 1.0 below than that for the *S*-enantiomer for **1c**. This difference increases to 2.1 for **1d**, in good agreement with the experimental higher stereoselectivity. It is attributable to a lack of unfavorable interactions between the proton-donor group and the C-5 substituent, which allows a more staggered C–C forming bond for the *Si*-face attack (45° for **1c** vs 39° for **1d**), and to the H-bond between the incipient carboxylated oxygen of the enamine of **1c** and the aromatic ring of the benzaldehyde in the formation of the *S*-enantiomer (Fig. 9).

In summary, the calculations provide a stereochemical model that rationalizes the experimental results. Thus, viable hydrogen-bond donors can stabilize the aldolisation transition state. The enantioselectivity is proposed to arise from intra- and intermolecular interactions in the staggered transition structures between the carbohydrate and the benzaldehyde. Our data suggest that subtle changes in both units can strongly affect the stereoselectivity outcome.

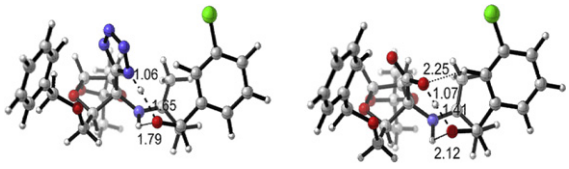


Fig. 9. Optimized transition structures for the attack of *anti*-enamine of **1d** (left) and **1c** (right) to the *Si*-face of 3-Cl–C_6H_4.

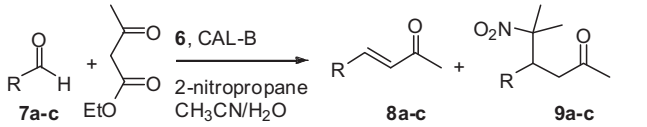
Next, we turned our attention to investigate our catalysts in a one-pot reaction including aldolisation and Michael addition starting from aldehydes. Asymmetric Michael additions of nitroalkanes to α,β-unsaturated ketones is one of the most powerful atom-economical carbon–carbon bond formation. The development of organocatalytic systems has been successfully applied to Michael addition.[27] For example, L-proline has been used for the addition of 2-nitropropane on aromatic α,β-unsaturated ketone but Et_3N (50 mol %) was necessary to achieve the reaction in 37% yield with <5% ee.[27a] Also, recently, Yu et al. demonstrated that immobilized *Candida antarctica* lipase B (CAL-B) lead in presence of aniline to α,β-unsaturated ketones starting from aromatic aldehydes via the formation of aldol derivatives.[28]

Keeping in mind those results, we undertook to use catalyst **6** in order to achieve the three steps sequence including, (i) CAL-B to

achieve the aldolisation reaction, (ii) an amino group in catalyst **6** to generate the α,β-unsaturated ketone, (iii) the α-aminotetrazole group in **6** for Michael addition.

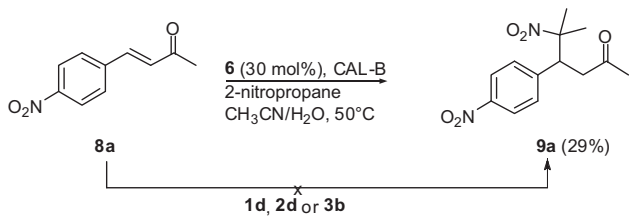
To realize the reaction, we replaced acetone by ethyl acetoacetate, which lead to the enolate through decarboxylation.[28] The results are summarized in Table 5. The different nitro-Michael compounds (**9a**–**c**) were obtained in modest yields (5–16%) and accompanied with the α,β-unsaturated ketone intermediate (**8a**–**c**). For all the nitro derivatives, the enantioselectivities are in the range 3–82% ee. Despite some modest results in this one-pot three steps sequence, catalyst **6** appears to be efficient in order to dehydrate the aldol product and to assist the Michael addition. This last was easily demonstrated in the direct addition of 2-nitropropane on the α,β-unsaturated ketone **8a** (Scheme 4). In this experiment, nitro derivative **9a** was obtained in 29% yield (vs 16% yield) demonstrating that the Michael addition step was the limiting step in the one-pot sequence. Moreover, the second amino group in catalyst **6** is essential because catalysts **1d**, **2d**, and **3b** in the same conditions could not afford the nitro-Michael addition. The α-aminotetrazole group could also be helpful in the aldolisation step as demonstrated in the first paragraph.

Table 5
One-pot aldolisation–Michael addition with ethyl acetoacetate catalyzed by CAL-B and **6**



Entry[a]	R	**8**, Yield[b] (%)	**9**, Yield[b] (%)	ee (%)[c,d]
1	4-$NO_2C_6H_4$	**8a** (16)	**9a** (16)	3 (*S*)
2	3-ClC_6H_4	**8b** (10)	**9b** (6)	70 (*R*)
3	2-Naphtyl	**8c** (29)	**9c** (5)	82 (*R*)

[a] Reaction conditions: **7** (0.66 mmol), ethyl acetoacetate (0.78 mmol), **6** (30 mol %), CAL-B 66 mg, 2-nitropropane/CH_3CN/H_2O ratio (2.8/1.0/0.04), 50 °C.
[b] Yield of product isolated by column chromatography.
[c] The ee value of the product was determined by HPLC analysis using a chiral column (chiralpak AD-H Daicel Chemical Industries).
[d] The absolute configuration was determined by comparison of the HPLC retention time of the product with reported data.



Scheme 4.

3. Conclusions

To sum up, a series of new and easily available glycosyl-based substituted tetrazoles have been prepared, and their efficiency in enantioselective aldol reactions clearly demonstrated, as high enantiomeric excesses and good to excellent yields have been obtained. Moreover, catalyst **6** showed interesting results in the one-pot three steps sequence including Michael addition. Despite some modest results in terms of yield, this example represents a promising collaboration between biocatalysis and organocatalysis few described in the literature and paved the way for further improvements. Regarding the structural diversity in carbohydrates, we believe that the α-aminotetrazole catalytic system can be supported by a wide range of sugar skeletons with a diversity of chiral centers.

Computational studies to account for the experimental observations reveal that the preferred transition structures involve stabilizing *anti*-enamine H-bond and that the enantioselectivity results from the steric and electrostatic interactions around the forming C–C bond. The *Re*-face attack generally features a more perfect staggering of substituents around the C–C bond as this attack mode poses the aryl group facing out, thus minimizing the steric interaction between the aldehyde substituent and the methyl or substituents of the sugar ring of the enamine.

4. Experimental section

4.1. Computational

Calculations were performed with Gaussian09.[29] All geometries were optimized using B3LYP/6-31G(2d,p). DFT calculations predict good transition state geometries.[30] The stationary points thus obtained were characterized by means of harmonic analysis, and for all the transition structures, the normal mode related to the imaginary frequency corresponds to the nuclear motion along the reaction coordinate under study. The vibrational zero-point and thermal corrections to the thermodynamic results were taken from the frequency calculations. The CPCM solvation model[31] was applied selecting the UAKS radii. Single-point calculations were performed on the B3LYP geometries[32] with M06/6-311+g(3d,2p). M06 provides more accurate selectivities and thermodynamic values and incorporates dispersion effects.[33]

4.2. General

Materials and methods. Melting points are uncorrected. Optical rotations were recorded in $CHCl_3$, CH_2Cl_2, acetone or H_2O solutions. ^1H NMR (300.13 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in $CDCl_3$, D_2O, DMSO-d_6 or MeOD-d_4 (internal Me_4Si), respectively. TLC was performed on Silica F_{254} and detection by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. FTIR spectra were obtained on a AVATAR™ 320 neat using ATR and are reported in cm^{-1}. Mass spectral data were acquired on a WATERS Micromass Q-TOFF spectrometer. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS-H columns were purchased from Daicel Chemical Industries. Column chromatography was effected on Silica Gel 60 (230 mesh). Cyclohexane and ethyl acetate were distilled before use.

*4.2.1. 5-O-Benzyl-1,2-O-isopropylidenespiro[3-deoxy-α-D-erythropentofuranose-3,5′-imidazolidine]-2′,4′-dione (**1b**).* To a solution of compound **1a** (8.0 g, 26.29 mmol) in MeOH (120 mL) was added $(NH_4)_2CO_3$ (24.0 g, 250 mmol) and H_2O (120 mL). After stirring at 70 °C for 1 h and cooling at room temperature, the reaction mixture was filtered and the solvent eliminated under reduced pressure. After flash chromatography (EtOAc/cyclohexane, 40/60), compound **1b** (8.7 g, 95%) was obtained as a syrup. $[\alpha]_D^{20}$ +68 (*c* 0.33, $CHCl_3$); IR (ATR) ν 2988, 2900, 1724, 1405, 1384, 1234, 1179, 1055 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 8.74 (s, 1H, NH), 7.21 (m, 5H, Ph), 6.08 (s, 1H, NH), 5.92 (d, $J_{1,2}$=3.7 Hz, 1H, H-1), 4.46 (d, 1H, H-2), 4.42 (s, 2H, OCH_2Ph),4.27 (t, $J_{4,5a}$=5.8 Hz, 1H, H-4), 3.70 (dd, $J_{5a,5b}$=10.4 Hz, 1H, H-5a), 3.57 (dd, $J_{4,5b}$=5.8 Hz, 1H, H-5b), 1.48, 1.28 (s, 6H, 2× CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.3 (CO), 156.6 (CO), 137.6, 128.8, 128.5, 128.2 (Ph), 114.0 [O*C*$(CH_3)_2$], 105.3 (C-1), 81.3 (C-2), 78.7 (C-4), 74.2 (OCH_2Ph), 71.2 (C-3), 68.0

(C-5), 27.1, 26.9 (2× CH_3); HRMS: $C_{18}H_{24}N_2O_5Na$ calcd 371.1583, found 371.1576.

*4.2.2. 1,2:5,6-Di-O-isopropylidenespiro[3-deoxy-α-D-ribo-hexofuranose-3,5′-imidazolidine]-2′,4′-dione (**2b**).* To a solution of compound **2a** (0.5 g, 1.76 mmol) in MeOH (10 mL) was added $(NH_4)_2CO_3$ (1.70 g, 17.6 mmol) and H_2O (10 mL). After stirring at 70 °C for 2 h and cooling at room temperature, the reaction mixture was filtered and the solvent eliminated under reduced pressure. After crystallization in diethyl ether, compound **2b** (0.56 g, 97%) was obtained as a solid. Mp=232–236 °C; $[\alpha]_D^{20}$ +56 (*c* 0.76, $CHCl_3$); IR (ATR) ν 2985, 2902, 1784, 1721, 1381, 1225, 1075, 1017 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 8.77 (s, 1H, NH), 6.16 (s, 1H, NH), 5.91 (d, $J_{1,2}$=3.6 Hz, 1H, H-1), 4.55 (d, 1H, H-2), 4.17 (ddd, $J_{4,5}$=9.1 Hz, 1H, H-5),4.06 (d, $J_{5,6a}$=3.4 Hz, 1H, H-6a), 3.96 (d, $J_{5,6b}$=3.4 Hz, 1H, H-6b), 3.96 (d, 1H, H-4), 1.54, 1.36, 1.33, 1.24 (s, 12H, 4× CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.1 (CO), 156.2 (CO), 113.6 [O*C*$(CH_3)_2$], 104.8 (C-1), 81.5 (C-2), 79.6 (C-4), 74.1 (C-5), 71.2 (C-3), 67.9 (C-6), 26.8, 26.6, 26.4, 24.8 (4× CH_3); HRMS: $C_{14}H_{20}N_2O_7Na$ calcd 351.1168, found 351.1168.

*4.2.3. 3-Amino-5-O-benzyl-3-C-carboxy-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**1c**).* To a solution of compound **1b** (3.13 g, 9.0 mmol) in H_2O (100 mL) was added $Ba(OH)_2 \cdot 8H_2O$ (8.50 g, 27.0 mmol). After stirring for 7 days at reflux, CO_2 was bubbling into the flask, then the reaction mixture was filtered and the salt washed with hot water. After removal of the solvent, the crude was purified by flash chromatography (EtOAc/MeOH/acetic acid, 80/19/1) to afford compound **1c** (2.63 g, 91%) as a solid. Mp=193–194 °C; $[\alpha]_D^{20}$ +13 (*c* 0.18, H_2O); IR (ATR) ν 2987, 2901, 1634, 1556, 1407, 1393, 1242, 1226, 1077 cm^{-1}; ^1H NMR (300.13 MHz, D_2O) δ 7.32 (m, 5H, Ph), 5.92 (d, $J_{1,2}$=3.6 Hz, 1H, H-1), 4.69 (s, 2H, OCH_2Ph), 4.48 (d, 1H, H-2), 4.10 (dd, $J_{4,5a}$=3.0 Hz, 1H, H-4), 3.66 (dd, $J_{5a,5b}$=11.0 Hz, 1H, H-5a), 3.45 (dd, $J_{4,5b}$=8.3 Hz, 1H, H-5b), 1.45, 1.28 (s, 6H, 2× CH_3); ^{13}C NMR (75.47 MHz, D_2O) δ 173.1 (CO), 137.4, 129.1, 128.9, 128.7 (Ph), 113.8 [O*C*$(CH_3)_2$], 106.0 (C-1), 82.4 (C-2), 81.3 (C-4), 73.7 (OCH_2Ph), 69.2 (C-5), 67.3 (C-3), 26.1, 25.7 (2× CH_3); HRMS: $C_{16}H_{21}NO_6Na$ calcd 346.1267, found 346.1282.

*4.2.4. 3-Amino-3-C-carboxy-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**2c**).* To a solution of compound **2b** (0.30 g, 0.86 mmol) in H_2O (12 mL) was added $Ba(OH)_2 \cdot 8H_2O$ (0.86 g, 2.73 mmol). After stirring for 7 days at reflux, CO_2 was bubbling into the flask, then the reaction mixture was filtered and the salt washed with hot water. After removal of the solvent, the crude was purified by flash chromatography (EtOAc/MeOH/acetic acid, 80/19/1) to afford compound **2c** (0.20 g, 72%) as a solid. Mp=173–175 °C; $[\alpha]_D^{20}$ +34 (*c* 0.22, H_2O); IR (ATR) ν 1643, 1555, 1376, 1253, 1217, 1071, 1003 cm^{-1}; ^1H NMR (300.13 MHz, D_2O) δ 5.90 (d, $J_{1,2}$=3.5 Hz, 1H, H-1), 4.75 (d, 1H, H-2), 4.11 (ddd, $J_{5,6a}$=6.4 Hz, 1H, H-5),4.02 (dd, $J_{6a,6b}$=8.8 Hz, 1H, H-6a), 3.91 (d, $J_{4,5}$=7.0 Hz, 1H, H-4), 3.86 (d, $J_{5,6b}$=4.7 Hz, 1H, H-6b), 1.47, 1.35, 1.29, 1.25 (s, 12H, 4× CH_3); ^{13}C NMR (75.47 MHz, D_2O) δ 172.9 (CO), 114.1 [O*C*$(CH_3)_2$], 110.5 [O*C*$(CH_3)_2$], 106.0 (C-1), 82.6 (C-2), 81.9 (C-4), 74.3 (C-5), 68.2 (C-3), 66.1 (C-6), 26.2, 25.9, 25.7, 24.2 (4× CH_3); HRMS: $C_{13}H_{21}NO_7Na$ calcd 326.1216, found 326.1220.

*4.2.5. 3-Amino-5-O-benzyl-3-deoxy-1,2-O-isopropylidene-3-C-(1H-tetrazol-5-yl)-α-D-ribofuranose (**1d**).* To a solution of **1a** (1.35 g, 4.43 mmol) in toluene (40 mL) was added Bu_2SnO (1.32 g, 5.31 mmol) and $TMSN_3$ (1.19 mL, 8.86 mmol). After stirring for 2 h at 100 °C, the solvent was removed and the residue was purified by flash chromatography (20/80 to 50/50 EtOAC/MeOH) to afford **1d** as a slight brown solid (1.02 g, 66%). Mp=97–99 °C; $[\alpha]_D^{20}$ +25 (*c* 0.12, $CHCl_3$); IR (ATR) ν 2975, 1508, 1378, 1217, 1162, 1086, 1026 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6) δ 7.30 (m, 5H, Ph), 6.16 (d, $J_{1,2}$=3.7 Hz, 1H, H-1), 4.92 (d, 1H, H-2), 4.48 (dd, $J_{4,5a}$=2.2 Hz, 1H, H-4), 4.40 (d, $J_{A,B}$=12.4 Hz, 1H H-A OCH_2Ph), 4.36 (d, 1H, H-B OCH_2Ph), 3.67 (dd, $J_{5a,5b}$=10.9 Hz, 1H, H-5a), 2.83 (dd, $J_{4,5b}$=7.5 Hz, 1H, H-5b), 2.50 (s, 2H, NH_2), 1.60, 1.35 (s, 6H, 2× CH_3); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 157.3 (C=N), 138.7, 129.1, 128.4 (Ph), 113.8 [O*C*$(CH_3)_2$], 105.6 (C-1), 83.0 (C-2), 80.2 (C-4), 73.3 (OCH_2Ph), 68.8 (C-5), 61.6 (C-3), 27.2, 27.1 (2× CH_3); HRMS: $C_{16}H_{21}N_5O_4Na$ calcd 370.1491, found 370.1494.

*4.2.6. 3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(1H-tetrazol-5-yl)-α-D-glucofuranose (**2d**).* To a solution of **2a** (6.8 g, 24.12 mmol) in toluene (50 mL) was added Bu_2SnO (6.60 g, 26.53 mmol) and $TMSN_3$ (6.46 mL, 48.24 mmol). After stirring for 2 h at 100 °C, the solvent was removed and the residue was purified by flash chromatography (20/80 to 50/50 EtOAC/MeOH) to afford **2d** as a white solid (5.49 g, 70%). Mp=94–95 °C; $[\alpha]_D^{20}$ +29 (*c* 0.15, acetone); IR (ATR) ν 2987, 2928, 2852, 1608, 1529, 1452, 1377, 1213, 1163, 1070, 1049, 1003 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6) δ 6.14 (d, $J_{1,2}$=3.5 Hz, 1H, H-1), 4.82 (d, 1H, H-2), 4.36 (d, $J_{4,5b}$=3.6 Hz, 1H, H-4), 4.00 (m, 1H, H-5), 3.05 (dd, $J_{5,6a}$=6.2 Hz, $J_{6a,6b}$=8.2 Hz, 1H, H-6a), 2.80 (t, $J_{5,6b}$=$J_{6a,6b}$=8.2 Hz, 1H, H-6b), 1.57, 1.36, 1.30, 1.17 (s, 12H, 4× CH_3); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 156.7 (C=N), 113.1, 108.2 [O*C*$(CH_3)_2$], 105.4 (C-1), 83.2 (C-2), 80.8 (C-4), 73.4 (C-5), 63.3 (C-6), 61.9 (C-3), 27.0, 26.9, 26.6, 25.3 (4× CH_3); HRMS: $C_{13}H_{22}N_5O_5$ calcd 328.1621, found 328.1623.

*4.2.7. 3-Amino-3-C-cyano-3-deoxy-1,2-O-isopropylidene-5-O-tert-butyldimethylsily-α-D-ribofuranose (**3a**).* To a solution of 1,2-*O*-isopropylidene-α-D-xylose (10.5 g, 55 mmol) in pyridine (150 mL) was added TBDMSCl (10 g, 66 mmol). After stirring for 3 h, the solvent was removed under vacuo and the residue extracted with CH_2Cl_2 and H_2O. The organic layer was dried over Na_2SO_4, filtered and evaporated to afford compound **3** (15 g, 88%) as a syrup, which was used in the next step without further purification. To a solution of compound **3** (15 g, 49 mmol) in CH_2Cl_2 (140 mL) was added molecular sieves (one spatula) and Ac_2O (18 mL, 183 mmol). The reaction mixture was heated at reflux then PDC (12.8 g, 34 mmol) was added portionwise. After 4 h and elimination of the solvent under vacuo, the residue was dissolved in EtOAc and filtered through a silica pad. Evaporation of the solvent afforded crude ulose in a quantitative yield (14.8 g, >99%), which was used the next step. Crude ulose (14.8 g, 49 mmol) was dissolved in a methanolic solution of ammonia (7 N, 150 mL) and $Ti(O^iPr)_4$ (28 mL, 93 mmol) was added. After stirring overnight at room temperature, TMSCN (7.9 mL, 59 mmol) was added and the reaction mixture was stirred for 15 h. After addition of water (<10 mL) and EtOAc, the solvent was removed under vacuo. EtOAc was added and the residue was filtered through a silica pad. After evaporation of the solvent, compound **3a** (14.6 g, 91%) was obtained as a white solid. Mp=35–37 °C; $[\alpha]_D^{20}$ +7 (*c* 1.19, CH_2Cl_2); IR (ATR) ν 2929, 1474, 1385, 1374, 1097 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) δ 5.91 (d, $J_{1,2}$=3.7 Hz, 1H, H-1), 4.70 (d, 1H, H-2), 4.07 (dd, $J_{4,5a}$=9.2 Hz, $J_{4,5b}$=13.9 Hz, 1H, H-4), 3.92–3.88 (m, 2H, H-5), 2.02 (br s, 2H, NH_2), 1.57, 1.36 (s, 6H, 2× CH_3), 0.90 (s, 9H, *t*-Bu), 0.13, 0.12 (s, 6H, 2× $SiCH_3$); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 118.7 (CN), 113.6 [O*C*$(CH_3)_2$], 104.1 (C-1), 83.4 (C-2), 80.8 (C-4), 62.7 (C-5), 26.6, 26.4 (2× CH_3), 25.9 (*t*-Bu), 18.3 (*Cq* *t*-Bu), −5.7, −5.6 (2× $SiCH_3$); HRMS: $C_{15}H_{28}N_2O_4SiNa$ calcd 351.1716, found 351.1709.

*4.2.8. 3-Amino-5-O-tert-butyldimethylsilyl-3-deoxy-1,2-O-isopropylidene-3-C-(1H-tetrazol-5-yl)-α-D-ribofuranose (**3b**).* To a solution of **3a** (5.5 g, 16.76 mmol) in toluene (50 mL) was added Bu_2SnO (4.59 g, 18.43 mmol) and $TMSN_3$ (4.50 mL, 33.52 mmol). After stirring for 2 h at 100 °C, the solvent was removed and the residue was purified by flash chromatography (20/80 to 50/50 EtOAC/

MeOH). After crystallization in EtOAc/cyclohexane, pure compound **3b** was isolated as a white solid (2.56 g, 41%). Mp=127–128 °C; $[\alpha]_D^{20}$ +50 (*c* 0.12, acetone); IR (ATR) *ν* 2953, 2856, 1599, 1525, 1464, 1388, 1375, 1253, 1217, 1163, 1078, 1024, 1003 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6) *δ* 6.10 (d, $J_{1,2}$=3.6 Hz, 1H, H-1), 4.84 (d, 1H, H-2), 4.26 (d, $J_{4,5b}$=8.3 Hz, 1H, H-4), 3.87 (d, $J_{5a,5b}$=11.7 Hz, 1H, H-5a), 2.81 (dd, 1H, H-5b), 1.56, 1.41 (s, 6H, 2× CH_3), 0.81 (s, 9H, *t*-Bu), 0.02 (s, 6H, 2× $SiCH_3$); ^{13}C NMR (75.47 MHz, DMSO-d_6) *δ* 156.4 (C=N), 112.9 [O*C*$(CH_3)_2$], 105.3 (C-1), 83.1 (C-2), 82.3 (C-4), 62.8 (C-5), 61.4 (C-3), 26.9, 26.8 (2× CH_3), 26.2 (*t*-Bu), 18.4 (C*q* *t*-Bu), −4.7, −4.8 (2× $SiCH_3$); HRMS: $C_{15}H_{30}N_5O_4Si$ calcd 372.2067, found 372.2077.

*4.2.9. 3-Amino-5-azido-3-C-cyano-3,5-dideoxy-1,2-O-isopropylidene-α-D-ribofuranose (**5**).* To a solution of 5-azido-1,2-*O*-isopropylidene-α-D-xylofuranose (24 g, 111.6 mmol) in CH_2Cl_2 (200 mL) was added molecular sieves (one spatula) and Ac_2O (36.7 mL, 390.7 mmol). The reaction mixture was heated at reflux then PDC (29.4 g, 78.1 mmol) was added portionwise. After 4 h and elimination of the solvent under vacuo, the residue was dissolved in EtOAc and filtered through a silica pad. Evaporation of the solvent afforded crude ulose in a quantitative yield, which was used in the next step. Crude ulose was dissolved in a methanolic solution of ammonia (7 N, 150 mL) and $Ti(O^iPr)_4$ (28 mL, 93 mmol) was added. After stirring overnight at room temperature, TMSCN (7.9 mL, 59 mmol) was added and the reaction mixture was stirred for 15 h. After addition of water (<10 mL) and EtOAc, the solvent was removed under vacuo. EtOAc was added and the residue was filtered through a silica pad. After evaporation of the solvent, compound **5** (14.6 g, 91%) was obtained as a white solid. Mp=133–134 °C; $[\alpha]_D^{20}$ +6 (*c* 0.17, CH_2Cl_2); IR (ATR) *ν* 3367, 3305, 2097, 1377, 1388, 1269, 1220, 1166, 1104, 1090, 1060, 1014 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$) *δ* 5.96 (d, $J_{1,2}$=3.7 Hz, 1H, H-1), 4.64 (d, 1H, H-2), 3.86 (dd, $J_{4,5a}$=7.2 Hz, $J_{4,5b}$=5.0 Hz, 1H, H-4), 3.76 (dd, $J_{5a,5b}$=12.8 Hz, 1H, H-5a), 3.63 (dd, 1H, H-5b), 1.95 (br s, 2H, NH_2), 1.56, 1.37 (s, 6H, 2× CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$) *δ* 117.8 (CN), 113.8 [O*C*$(CH_3)_2$], 104.1 (C-1), 83.0 (C-2), 80.0 (C-4), 61.8 (C-3), 50.7 (C-5), 26.6, 26.4 (2× CH_3); HRMS: $C_9H_{14}N_5O_3$ calcd 240.10912, found 240.10930.

*4.2.10. 3-Amino-3-deoxy-1,2-O-isopropylidene-3-C-(1H-tetrazol-5-yl)-5-O-trityl-α-D-ribofuranose (**4a**).* To a solution of **4** (0.75 g, 1.64 mmol) in toluene (20 mL) was added Bu_2SnO (0.45 g, 1.81 mmol) and $TMSN_3$ (0.44 mL, 3.29 mmol). After stirring for 2 h at 100 °C, the solvent was removed and the residue was purified by flash chromatography (20/80 to 70/30 EtOAC/MeOH)to afford compound **4a** as a white solid (0.47 g, 57%). Mp=78–79 °C; $[\alpha]_D^{20}$ +15 (*c* 0.15, acetone); IR (ATR) *ν* 1597, 1491, 1448, 1377, 1217, 1163, 1070, 1003 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6) *δ* 7.30 (m, 15 H, 3× Ph), 6.07 (s, 1H, H-1), 4.69 (s, 1H, H-2), 4.31 (d, $J_{4,5a}$=9.0 Hz, 1H, H-4), 3.86 (br s, 4 H, H-5a, NH, NH_2), 3.25 (d, $J_{5a,5b}$=12.0 Hz, 1H, H-5b), 1.61, 1.37 (s, 6H, 2× CH_3); ^{13}C NMR (75.47 MHz, DMSO-d_6) *δ* 158.1 (C=N), 144.1, 128.7, 128.3, 127.4 (3× Ph), 112.2 [O*C*$(CH_3)_2$], 105.2 (C-1), 86.5 (C*q* trityl), 83.9 (C-2), 82.1 (C-4), 63.7 (C-5), 61.7 (C-3), 27.2, 27.0 (2× CH_3); HRMS: $C_{28}H_{29}N_5O_4Na$ calcd 522.2117, found 522.2138.

*4.2.11. 3-Amino-5-azido-3,5-dideoxy-1,2-O-isopropylidene-3-C-(1H-tetrazol-5-yl)-α-D-ribofuranose (**5a**).* To a solution of **5** (5.0 g, 20.92 mmol) in toluene (100 mL) was added Bu_2SnO (5.72 g, 23.01 mmol) and $TMSN_3$ (6.16 mL, 46.02 mmol). After stirring for 2 h at 100 °C, the solvent was removed and the residue was purified by flash chromatography (20/80 to 40/60 EtOAC/MeOH) to afford compound **5a** as a slight yellow solid (5.91 g, 99%). Mp=137–138 °C; $[\alpha]_D^{20}$ +78 (*c* 0.31, acetone); IR (ATR) *ν* 2989, 2929, 2098, 1602, 1510, 1377, 1265, 1222, 1163, 1080 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6) *δ* 6.12 (d, $J_{1,2}$=6.0 Hz, 1H, H-1), 5.66 (br s, 3H, NH, NH_2), 4.83 (d, 1H, H-2), 4.31 (d, $J_{4,5b}$=9.0 Hz, 1H, H-4), 3.43 (d, $J_{5a,5b}$=15.0 Hz, 1H, H-5a), 2.64 (dd, 1H, H-5b), 1.55, 1.36 (s, 6H, 2× CH_3); ^{13}C NMR (75.47 MHz, DMSO-d_6) *δ* 157.3 (C=N), 112.8 [O*C*$(CH_3)_2$], 105.3 (C-1), 83.5 (C-2), 80.9 (C-4), 62.1 (C-3), 50.7 (C-5), 27.0, 26.9 (2× CH_3); HRMS: $C_9H_{14}N_8O_3Na$ calcd 305.1087, found 305.1075.

*4.2.12. 3,5-Diamino-3,5-dideoxy-1,2-O-isopropylidene-3-C-(1H-tetrazol-5-yl)-α-D-ribofuranose (**6**).* To a solution of **5a** (1.0 g, 3.54 mmol) in 20 mL of a mixture of THF/H_2O (4/1) was added PPh_3 (1.02 g, 3.90 mmol). After stirring at room temperature overnight, the solvent was eliminated under vacuo. After extraction with water and diethyl ether (×3) and elimination of H_2O from the aqueous layer, a methanolic solution of ammonia (7 N, 100 mL) was added. After stirring overnight at room temperature, the solvent was eliminated under vacuo. After extraction with water and EtOAc (×2) and elimination of water under vacuo, compound **6** (0.47 g, 52%) was obtained as an amorphous solid. $[\alpha]_D^{20}$ +53 (*c* 0.45, acetone); IR (ATR) *ν* 2987, 2933, 2100, 1593, 1533, 1514, 1454, 1375, 1217, 1163, 1086 cm^{-1}; ^1H NMR (300.13 MHz, DMSO-d_6) *δ* 6.18 (d, $J_{1,2}$=3.0 Hz, 1H, H-1), 4.92 (br s, 5H, NH, 2× NH_2), 4.78 (d, 1H, H-2), 4.21 (dd, $J_{4,5a}$=3.0 Hz, $J_{4,5b}$=9.0 Hz, 1H, H-4), 3.03 (dd, $J_{5a,5b}$=15.0 Hz, 1H, H-5a), 2.34 (dd, 1H, H-5b), 1.63, 1.44 (s, 6H, 2× CH_3); ^{13}C NMR (75.47 MHz, DMSO-d_6) *δ* 160.4 (C=N), 112.2 [O*C*$(CH_3)_2$], 105.1 (C-1), 84.4 (C-2), 80.1 (C-4), 62.7 (C-3), 39.6 (C-3), 25.6, 25.2 (2× CH_3); HRMS: $C_9H_{16}N_6O_3Na$ calcd 279.1192, found 279.1187.

*4.2.13. 4-(4-Nitrophenyl)-3-buten-2-one (**8a**) and 4-(4-nitrophenyl)-5-methyl-5-nitrohexan-2-one (**9a**).* To a solution of the aldehyde **7a** (0.66 mmol) in 325 μL of a mixture of CH_3CN/H_2O (87/13) was added 99 μL (0.78 mmol) of ethyl acetoacetate, 66 mg of CAL-B immobilized on acrylic resin, 30 mol % of **6** (51 mg, 0.2 mmol) and 795 μL of 2-nitropropane (14 mmol). The suspension was stirred for 5 days at 50 °C. The reaction was then concentrated under reduced pressure and the crude material was purified by flash chromatography using cyclohexane/EtOAc (100/0 to 90/10) to afford successively **8a**[34] (20 mg, 16%) as a white solid and **9a**[35] (30 mg, 16%) as a pale yellow solid. Enantiomeric excess of **9a** was determined by chiral HPLC (AD-H column, 8/2 hexane/^{i}PrOH, flow rate 1 mL/min, t_{major}=16.0 min, t_{minor}=24.3 min, *λ*=254 nm).

*4.2.14. 4-(3-Chlorophenyl)-3-buten-2-one (**8b**) and 4-(3-chlorophenyl)-5-methyl-5-nitrohexan-2-one (**9b**).* To a solution of the aldehyde **7b** (0.66 mmol) in 325 μL of a mixture of CH_3CN/H_2O (87/13) was added 99 μL (0.78 mmol) of ethyl acetoacetate, 66 mg of CAL-B immobilized on acrylic resin, 30 mol % of **6** (51 mg, 0.2 mmol) and 795 μL of 2-nitropropane (14 mmol). The suspension was stirred for 5 days at 50 °C. The reaction was then concentrated under reduced pressure and the crude material was purified by flash chromatography using cyclohexane/EtOAc (100/0 to 90/10) to afford successively **8b**[36] (13 mg, 10%) as a pale yellow liquid and **9b**[27d] (11 mg, 6%) as a pale yellow solid. Enantiomeric excess of **9b** was determined by chiral HPLC (AD-H column, 99/1 hexane/^{i}PrOH, flow rate 1 mL/min, t_{major}=22.4 min, t_{minor}=28.1 min, *λ*=254 nm).

*4.2.15. 4-(2-Naphtalenyl)-3-buten-2-one (**8c**) and 4-(2-naphtalenyl)-5-methyl-5-nitrohexan-2-one (**9c**).* To a solution of the aldehyde **7c** (0.66 mmol) in 325 μL of a mixture of CH_3CN/H_2O (87/13) was added 99 μL (0.78 mmol) of ethyl acetoacetate, 66 mg of CAL-B immobilized on acrylic resin, 30 mol % of **6** (51 mg, 0.2 mmol) and 795 μL of 2-nitropropane (14 mmol). The suspension was stirred for 5 days at 50 °C. The reaction was then concentrated under reduced pressure and the crude material was purified by flash chromatography using cyclohexane/EtOAc (100/0 to 90/10) to afford successively **8c**[34] (30 mg, 29%) as a pale yellow liquid and **9c** (10 mg, 5%) as a pale yellow solid. Enantiomeric excess of **9c** was determined by chiral HPLC (AD-H column, 8/2 hexane/^{i}PrOH, flow rate 1 mL/min, t_{major}=7.2 min, t_{minor}=6.3 min, *λ*=254 nm). Compound **9c**: ^1H

NMR (300.13 MHz, $CDCl_3$) δ (ppm) 7.82–7.78 (3H, m, H_{aro}), 7.66 (1H, d, J=1.7 Hz, H_{aro}), 7.50–7.46 (2H, m, H_{aro}), 7.32 (1H, dd, J=1.9 Hz, J=8.5 Hz, H_{aro}), 4.11 (1H, dd, J=3.5 Hz, J=10.6 Hz, C*H*), 3.22 (1H, dd, J=10.6 Hz, J=17.0 Hz, H_a CH_2), 2.80 (1H, dd, J=3.5 Hz, J=17.0 Hz, H_b CH_2), 2.03 (3H, s, CH_3CO), 1.61, 1.53 (3H, s, $CH_3(CNO_2)$), ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 205.3 (CO), 143.66 (=C–CH*), 129, 128.9, 128.6, 128.5, 128.2, 127.8, 127.2, 126.6, 126.5 (C_{aro}), 91.4 (CNO_2), 49.21(CH*), 44.48 (CH_2), 30.59 (CH_3CO), 26.35, 22.78 (CH_3–CNO_2); HRMS: $C_{17}H_{19}NO_3Na$ calcd 308.1263, found 308.1270.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.04.043.

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