An unusual stereoselectivity in the anomeric substitution with carbamates promoted by $HNTf_2$†‡

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An unexpected stereoselective anomeric substitution with carbamates promoted by $HNTf_2$ is described here. Our experiments suggest that the observed diastereoselectivity is a result of thermodynamic equilibration of protonated *N*-acyl aminals.

Anomeric substitutions represent one of the most important chemical transformations.[1] The leaving-group [L in **1**] can be activated with a Brønsted acid, Lewis acid [LA], or transition metal [M] to give oxocarbenium ions **2** [Fig. 1], and to complete the substitution, a nucleophilic addition can occur at either *Re* or *Si* face to afford **3a** or **3s**. The stereochemical outcome can be controlled through an anomerically favored axial addition to a preferred conformation of **2**.[1–3] Oxocarbenium ions **2** with two or more R substituents [$n = 1$ through 4] can possess a distinct advantage in the conformational control that can lead to a high level of stereoselectivity.[1] It is not until recently,[4–6] that one gains a more comprehensive understanding of fundamental issues in anomeric substitutions when there is a minimum number of R substituents [$n = 1$].[4–6]

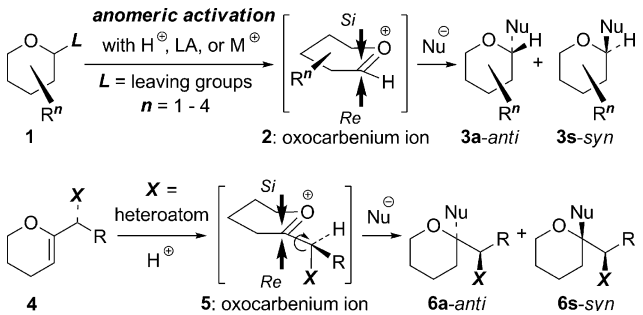
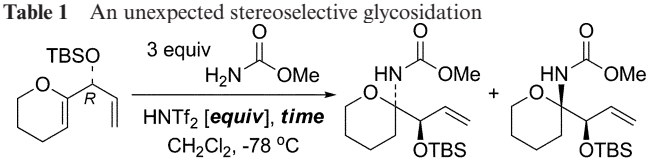


Fig. 1 Stereochemical control in anomeric substitutions.

In our pursuit of cyclic ketal- or aminal-tethered reactions[7–9] as a new strategy for the synthesis of spiroketals or spiroaminals,[10] we encountered another possible mode of stereochemical control in anomeric substitutions through oxocarbenium ions **5** in which the existing stereocenter is conformationally flexible and *exo*-cyclic to the ring, and contains a heteroatom [X]. We report here our observations of an unexpected stereochemical outcome in a Brønsted acid promoted anomeric substitution with carbamates.

Table 1 An unexpected stereoselective glycosidation



Entry	Acid/equiv.	Time/min	Yield[a] [%]	Dr[b]: **a** : **s**
1	0.01	1140[c]	39	1.6 : 1
2	0.10	60	64	2.3 : 1
3	0.25	60	70	5.8 : 1
4	0.50	30	66	6.5 : 1
5	1.0	30	73	10.3 : 1
6	1.0	5[c]	48	2.4 : 1
7	1.5	15	75	21.8 : 1
8	2.0	15	77	40 : 1
9	3.0	15	60	50 : 1

[a] Isolated yields. [b] Ratios by ^1H or ^{13}C NMR. [c] At −35 °C.

During the preparation of cyclic aminals from dihydropyran **7** and *O*-methyl carbamate employing $HNTf_2$[11] as a Brønsted acid catalyst[12] [Table 1], we noticed that the resulting cyclic aminal **8**[13] appeared to have a gradual but noticeable increase in the diastereomeric ratio as the amount of $HNTf_2$ was increased. Specifically, the ratio would rise from 2.3 : 1 with 0.10 equiv. of $HNTf_2$ [entry 2] to ≥50 : 1 when using 3.0 equiv. of $HNTf_2$ [entry 9]. The major isomer was unambiguously assigned as being *anti* based on the X-ray structure of **9a** (Fig. 2), which was prepared from the addition of *O*-benzyl carbamate to **7**.

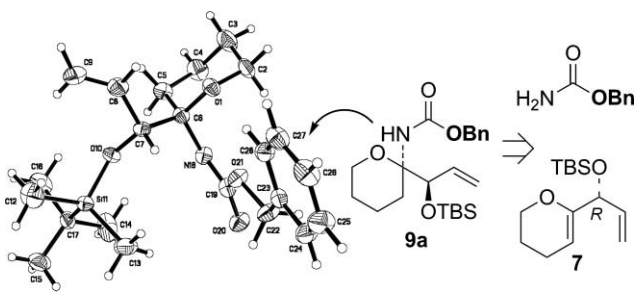


Fig. 2 X-Ray structure of **9a**: There are two independent molecules in the asymmetric unit of **9a** and only one of the two is shown (ellipses at 50% probability).

It was quickly evident that this interesting phenomenon is associated with $HNTf_2$. Brønsted acids TFA, CSA, *p*-TsOH, and 2,4-dinitrobenzenesulfonic acid not only were ineffective for

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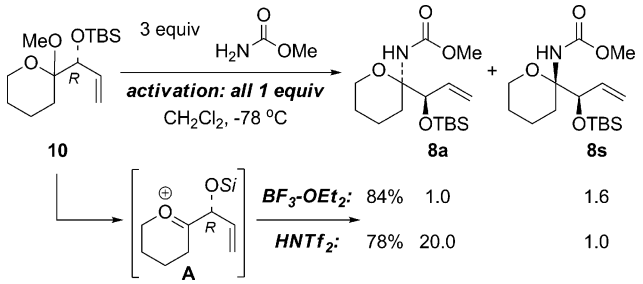
† The authors wish to dedicate this paper to Professor Gilbert Stork on the very special occasion of his 85th birthday.

‡ Electronic supplementary information (ESI) available: Experimental details and spectral data, and NMR spectra for all new compounds. See DOI: 10.1039/b615725d

promoting the cyclic aminal formation at −78 °C, but also when the reaction did proceed at −35 °C, these acids led to cyclic aminals **8a** and **8s** in low yields [10–30%] with low ratios [1.6–3.0 : 1], albeit still in favor of **8a**.

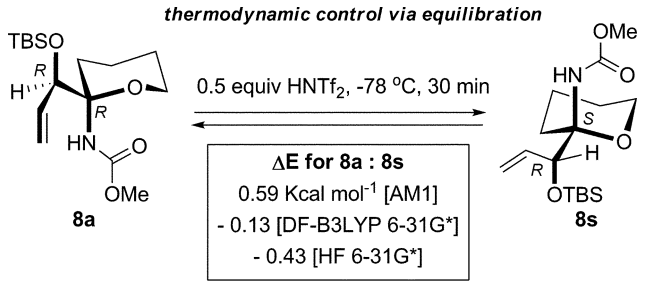
In addition, when the oxocarbenium ion **A** was generated from cyclic acetal **10** using BF_3–OEt_2, the resulting cyclic aminals **8a** and **8s** were obtained with an *anti* : *syn* ratio of 1 : 1.6 [Scheme 1]. On the other hand, by employing $HNTf_2$, acetal **10** still led to cyclic aminals **8a/s** with a high ratio, thereby further implying the significance of $HNTf_2$ and not how the oxocarbenium intermediate was generated.



Scheme 1 Significance of $HNTf_2$.

With $HNTf_2$ emerging as a unique Brønsted acid in promoting a range of transformations,[11,12] and given the recent interest in the Brønsted acid catalysis,[14] we decided to investigate the origin of this unusual stereochemical observation. We initially thought the unexpected stereoselectivity was a kinetic phenomenon especially when ^{1}H NMR revealed an initial ratio of [4–5 : 1] for **8a** : **8s** at −78 °C.[15] However, we quickly found that products equilibrate under the reaction conditions [Scheme 2], thereby suggesting a thermodynamic control.

At the same time, what then further intrigued us was that calculations of ΔE [$E^{8a} - E^{8s}$] *via* three separate methods appear to indicate otherwise [see the box in Scheme 2]. The calculations using DF-B3LYP6-31G* and HF-6-31G* actually show that **8s** is slightly favored. With these conflicting results in hand, we examined another possibility that would involve protonations of cyclic aminal products given that $HNTf_2$ is a powerful Brønsted acid[16] and the carbamate carbonyl oxygen atom is a good Lewis base.



ratio of	initial	final	recovery yields
8a : 8s	100 : 0	9.4 : 1	70%
	50 : 50	9.5 : 1	67%
	0 : 100	7.2 : 1	65%

Scheme 2 A proposed mechanistic model.

As shown in Fig. 3, ΔE^* [$E^{8a}* - E^{8s}*$] of protonated-**8a** and **8s** [or denoted as **8a*** and **8s***] using the same three methods revealed that **8a*** is now by far more favored. Furthermore, models illustrate that the proton bound to the carbonyl oxygen [in bold] appears to be within the proximity to hydrogen bond with the oxygen atom of the OTBS group in the *anti* isomer **8a*** [also in bold], while with the pyranyl oxygen atom in the *syn* isomer **8s*** [in bold italics], which is in a boat conformation.

These calculations suggest that the observed diastereoselectivity is likely a result of thermodynamic equilibration of protonated cyclic aminals. This mechanistic assessment is consistent with the observation that while the reaction is catalytic in $HNTf_2$, greater ratios were observed only when more $HNTf_2$ was employed to ensure sufficient protonation of products.

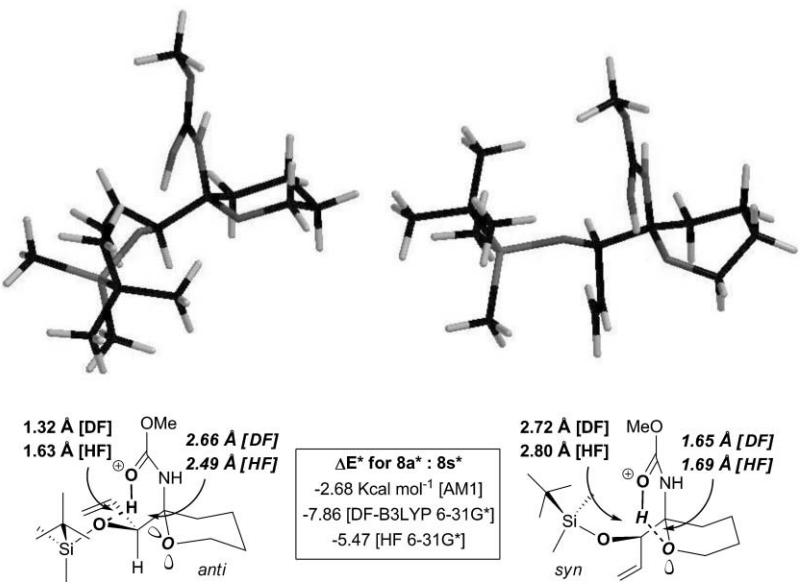
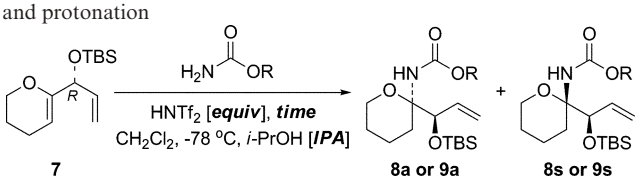


Fig. 3 Equilibration through the protonated forms.

Table 2 Competing hydrogen bonding and protonation



Entry	Equiv. carbamate	$HNTf_2$	IPA	t/min	R	Yield[a] [%]	Dr[b]: **a** : **s**
1	1.0 [0.5 : 1]	2.0	—	15	Me	8 : 68	50 : 1
2	1.0 [1 : 1]	1.0	—	30	Me	8 : 64	24.4 : 1
3	6.0 [3 : 1]	2.0	—	15	Me	8 : 66	9.6 : 1
4	6.0 [6 : 1]	1.0	—	30	Me	8 : 63	8.6 : 1
5	1.0	1.0	—	30	Bn	9 : 61	38.2 : 1
6	1.0	1.0	1.0	30	Bn	9 : 63	10.4 : 1
7	1.0	1.0	3.0	30	Bn	9 : 61	2.7 : 1
8	1.0	1.0	6.0	30	Bn	ND[c]	ND

[a] Isolated yields. [b] Ratios from ^1H and/or ^{13}C NMR. [c] ND: not determined.

Nevertheless, we pursued the following studies to further support the model. As shown in Table 2, we quickly found that the ratio of carbamate : $HNTf_2$ can impact on the selectivity [entries 1–4] with a higher amount of carbamate providing lower ratios. This implies that excess of carbamate can compete with products for available protons, thereby shifting the energetic difference between the protonated cyclic aminals **8a*** and **8s***.

In addition, as an equivalent of solvent effect on the selectivity, we examined additives such as *i*-PrOH [IPA] and found that IPA also assumes a similar role in competing for protons and disrupting the proposed energetic equilibrium [entries 5–8]. With the carbamate : $HNTf_2$ ratio fixed at 1 : 1, the ratio was found to decrease with increasing amount of IPA, and 6 equiv. of IPA actually shut down the reaction [entry 8]. These experiments are again consistent with the proposed model in which the stereoselectivity is a result of thermodynamic equilibration of protonated cyclic aminals.

We have communicated here an unexpected stereoselective anomeric substitution with carbamates promoted by $HNTf_2$. Efforts in achieving a complete mechanistic understanding and developing useful synthetic methods as well as *N*-glycosidation protocols based on this unexpected observation are currently under way.

Acknowledgements

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wR_2 = 0.2237. Largest diff. peak and hole [_refine_diff_density_max] = 1.200 and −0.317 e Å^{-3}. CCDC reference number 625894. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b615725d.

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16 Additions of ROH to construct related cyclic ketals employing $HNTf_2$ led to low ratios [∼1.5–2 : 1] as well.

