Inverted regioselectivity of C–H amination: Unexpected oxidation at β- rather than γ-C–H†

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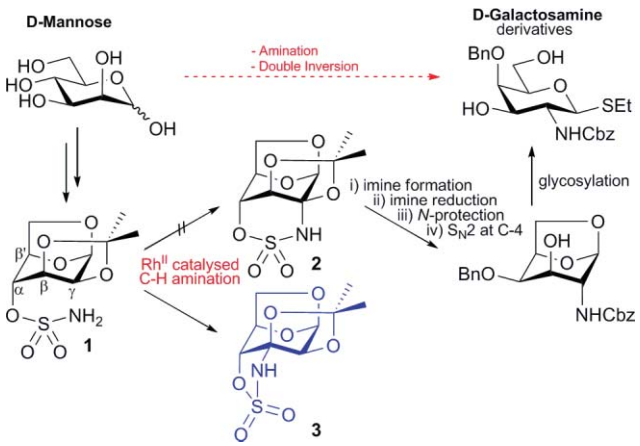
A rare example of β- over γ-C–H selectivity during Rh-catalysed sulfamate ester cyclisation is presented; from derivatives of 1,6-anhydro-β-D-mannopyranose, five-membered sulfamidates were formed in preference to the typical six-membered oxathiazinane intramolecular insertion products. A 3D structure of sulfamate 1 helps to rationalise this unusual selectivity and analyses suggest that n→σ*(CH) interactions may be a key controlling factor.

Selective functionalisation of C–H bonds has commanded widespread attention from organic chemists, offering an efficient alternative to the activated handles often required for performing complex synthetic transformations.[1] Tremendous advances have been made over the last decade,[2] notably in the transition metal catalysed amination of unactivated C–H bonds.[3] Du Bois *et al.* pioneered the use of carbamates and sulfamate esters for this purpose, which upon exposure to Rh^{II} and an oxidant give access to 1,2- and 1,3-difunctionalised amine derivatives.[4] Site selectivity has been directed by exploiting the greater reactivity of ethereal C_α–H bonds to metal-nitrene and -carbene species, as well as the preference for tertiary rather than secondary C–H bonds.[4,5] Conformational control also steers selectivity, with carbamates giving five-membered ring insertion products and sulfamate esters forming six membered rings.[4,6] This exclusive γ-C–H bond amination is accounted for by the elongated S–O and S–N bonds (1.58 Å) and the obtuse angle of the N–S–O motif in the sulfamate (103°), which match the metric parameters of the six-membered oxathiazinane product and thus make the formation of a 5-membered ring less kinetically favourable.[4] Although rare cyclisation to a five-membered oxathiazolidine product has been observed, this has only been in the absence of any possible γ insertion pathway[4,7] or if the β-C–H bond has been selectively activated over the γ position with an α-electron donating group,[8] with the single exception of a low-yielding cyclisation of an unfunctionalised cyclopentyl sulfamate ester.[9] Cyclisation to 7 and 8-membered sulfamidates has been reported, but again only when driven by the presence of a heteroatom adjacent to the site of insertion for specific C–H activation.[10]

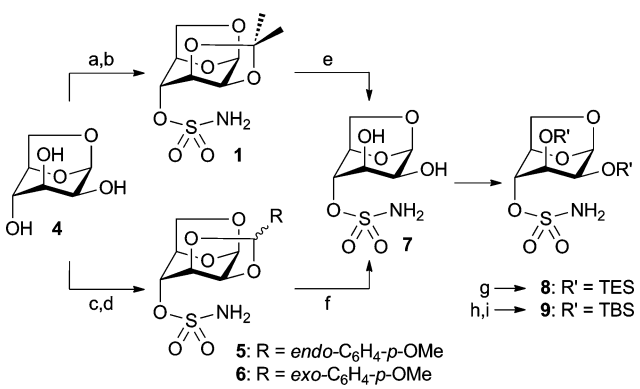
In an attempt to create ready access to 2-amino-2-deoxy-D-galactose derivatives[11,12] and other aminosugars we explored a novel synthetic route, utilising C–H amination methodology (Scheme 1). By creating 1,6-anhydro-β-D-mannose derivatives locked in an atypical $^1C_4$ conformation, we postulated that the



Scheme 1 Unexpected regioselectivity upon C–H amination of **1**.

γ-C–H would be brought into close proximity of the sulfamate nitrogen for subsequent Rh^{II}-catalysed oxidative cyclisation. Further derivatisation of the resulting *N*,*O*-acetal would lead to selectively protected galactosamine derivatives; starting material D-mannose having undergone an overall process of configurational inversion at both C-2 and C-4 and a selective amination.

To test out this approach, we synthesised acetonide sulfamate **1** through regioselective acetal formation followed by sulfamoylation (Scheme 2) and exposed it to C–H amination conditions. Unexpectedly, exclusive cyclisation to five-membered sulfamidate **3** was observed, foregoing any reaction at the seemingly more favourable γ-C^2–H (to give **2**) or indeed the equivalent β′-C^5–H.



Scheme 2 Synthesis of differentially protected 1,6-anhydro-D-mannose sulfamate esters. *Reagents and conditions*: (a) see ref. 13; (b) $ClSO_2NH_2$, Et_3N, DMA, –10 °C, 80%; (c) anisaldehyde dimethylacetal, TsOH, DMF, 50 °C, 300 mbar; (d) $ClSO_2NH_2$, Et_3N, DCM, –10 °C, 61% **5** (over 2 steps), **6** see discussion; (e) TFA/H_2O 4 : 1, 100%; (f) TsOH, MeOH, 77%; (g) TESCl, imidazole, 1,4-dioxane, 36%; (h) TBSCl, imidazole, DMA; (i) TFA–THF–H_2O 1 : 10 : 5, 0 °C, 51% (over 2 steps).

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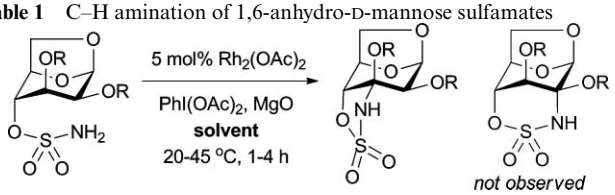
Table 1 C–H amination of 1,6-anhydro-D-mannose sulfamates



Entry[a]	R	Solvent	Product	Conv. (%)
1	–C(Me)$_2$–	THF[b]	**3**	45[c]
2	–CH(*endo*-*p*-MeOC$_6$H$_4$)–	1,4-Dioxane	**10**	92
3[d]	–CH(*exo*-*p*-MeOC$_6$H$_4$)–	1,4-dioxane	**11**	49[e]
4	TES	DCM	**12**	19
5	TBS	DCM	**13**	61
6	H	1,4-Dioxane	—	0

[a] Reactions performed with 0.2M sulfamate, 5 mol% $Rh_2(OAc)_2$, 2.3 eq MgO and 1.1 eq $PhI(OAc)_2$. [b] 0.05M sulfamate used. [c] 54% starting material recovered. [d] Reaction performed on *exo*-enriched **5** + **6** mixture (2 : 1). [e] Determined from ^{1}H NMR analysis of isolated product mixture.

This was especially surprising since all three possible insertion sites are potentially activated as tertiary α-ethereal centres.

To probe this unusual selectivity we replaced the acetonide in **1** with a selection of different protecting groups to explore possible increased conformational flexibility that might encourage reversion to the expected γ-C–H insertion pathway (Scheme 2). 1,6-Anhydro-β-D-mannose[13] was reacted with anisaldehyde dimethyl acetal and TsOH under reduced pressure, giving a stereoisomeric mixture of 2,3-*O*-acetals. Following purification, the *endo* isomer was selectively crystallised in 31% yield, leaving an *exo*-enriched mother liquor (*endo*/*exo* 1 : 2) in a 59% combined yield. These acetals were next converted to sulfamate esters **5** and a mixture of **5** + **6** in 76% and 46% yields respectively under standard conditions. In order to access acyclic protection of the 2- and 3- hydroxyls, acetals **1** and **5** + **6** were cleaved with acid hydrolysis in quantitative and 77% yields respectively. We next screened a variety of conditions to selectively derivatise the resulting diol **7** in the presence of the sulfamate ester. Acetyl protection proved unsuitable owing to equivalent reactivity of the hydroxyls and sulfamate nitrogen, so silyl protection was instead chosen; Si–N bonds are known to be significantly more labile than Si–O bonds.[14] Di-TES **8** and di-TBS **9** derivatives were accessed in 36 and 46% yields respectively, following selective deprotection of an *N*-TBS derivative with TFA in wet THF.

With six differently protected sulfamates in hand, these 1,6-anhydro-D-mannose derivatives were exposed to C–H amination conditions (Table 1). All of the substrates successfully underwent sulfamate insertion with the exception of diol **7**; the free hydroxyls presumably protonate the basic nitrene species (Entry 6).[15] It was found that a high concentration of sugar was required for efficient conversion; fortunately the reaction was tolerant to a number of aprotic solvents allowing the reaction solvent to be optimised based on the solubility profile of individual substrates. With the anisaldehyde acetal derivatives, the *endo* isomer was converted to the insertion product **10** in 92% yield (Entry 2). The *exo* isomer was reacted as an *exo*-enriched mixture of acetal isomers, and a single spot by TLC was isolated in 49% yield. The NMR contained two distinct products, in the same 2 : 1 ratio as the epimeric mixture of starting materials. The minor compound corresponded exactly to the *endo* product **10**, suggesting that the other was derived from the *exo* sulfamate **6**, allowing the *exo* product to be successfully assigned (Entry 3). Lower yields were observed with the di-TES derivative **8** resulting from losses during flash chromatography caused by the lability of the *O*-TES ethers (Entry 4).

Crucially, careful analysis of the NMR spectra obtained from all the sulfamidate products confirmed *N*-insertion had once again taken place at C-3 rather than C-2 – clear $^3J_{1\text{-}2}$ couplings of ~2 Hz were observed alongside a lack of any $^3J_{2\text{-}3}$ or $^3J_{3\text{-}4}$ couplings. COSY and HMBC analysis further confirmed these assignments. No formation of six-membered oxathiazinanes was detected in any of the examples. It appears that putative conformational changes imposed by the different protecting groups had little or no effect on the β-selectivity of C–H amination.

In the X-ray crystal structure‡ of acetonide sulfamate **1** (Fig. 1), structural analysis sheds further light on the unusual regioselectivity observed. The C–H bonds at C-2, C-3 and C-5 are all accessible to the sulfamate nitrogen. Data from the crystal structure would suggest insertion at C-2 – the S–O4 and S–N bond lengths are 1.5930(10) and 1.5921(12) Å respectively and the O4–S–N angle is 101.75(6)°, closely matching previous data and thus favouring attack at the tertiary, α-ethereal γ-C–H bond.[4] Therefore, it is especially surprising that only β-C–H insertion products are observed. In the case of acetal-protected sulfamates, it is possible that cyclization onto C-2 would produce a highly strained tetracyclic cage; the 5-membered cyclization product may provide a lower energy pathway with the new ring formed both minimising the strain imposed on the core pyranoside and avoiding repulsion between sulfoxide and pyranose oxygen lone pairs. This may also explain why the identity and/or stereochemistry of the acetal protecting group – which was expected to impose small conformational changes – had no bearing on the regioselectivity of the insertion reaction. In particular, the silylated sulfamates **8** and **9** were expected to show greater flexibility. Again, however, these sulfamates cyclized exclusively at C-3, showing no evidence of any reaction at C-2 or C-5.

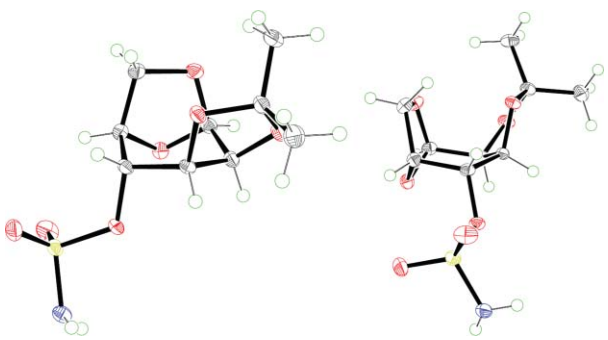


Fig. 1 Thermal ellipsoid plot of acetonide sulfamate **1** drawn at 50% probability.

There are several potential origins of this clear selectivity. The rigid bi- or tricyclic scaffold might present the β-C^3–H bond in a much more favourable conformation for nitrene insertion than the γ-C^2–H bond. The crystal structure does indeed show the pyranose ring to be distorted away from a chair conformation, leaving the axial bonds at C-2 and C-4 no longer parallel but pointing slightly away from each other: the H–C2–C4–O torsion angle is 2.6° and the angle between C2–H and C4–O vectors is 28.0°. A potential dominating effect consistent with the observed specificity of attack

at C-3 over C-5 can be considered through stereoelectronic effects. Both C–H bonds are β to the sulfamate and both show similar spatial orientation relative to C^4–O. However, the C^3–H bond is selectively weakened by hyperconjugation from the adjacent oxygen lone pair, which is held in a suitable conformation to overlap well with the C^3–H σ* orbital (Fig. 2). In contrast, the lone pair orbitals of the pyranose oxygen are more poorly aligned with σ*(C^5–H), making this bond less activated for nitrene insertion.

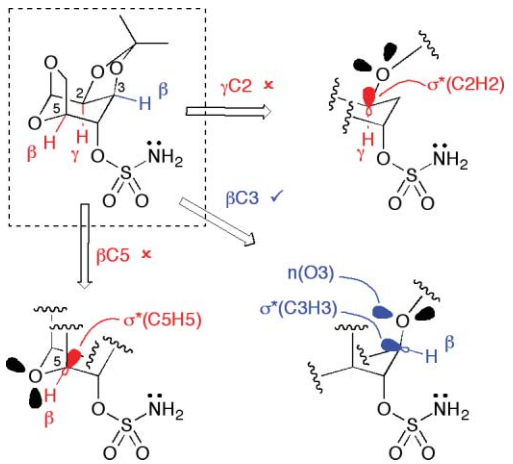


Fig. 2 Stereoelectronic analysis of observed regioselectivity in C–H insertion amination.

In conclusion, to the best of our knowledge this is the first example of a high-yielding and regioselective sulfamate cyclisation leading to the formation of a five membered ring in preference to a six membered ring. Key factors appear to involve an effective n→σ* hyperconjugative interaction. This interesting and unique observation on selectivity factors in C–H insertion will further understanding of the influencing factors and mechanistic aspects involved in C–H activation and nitrene insertion methodologies, helping to direct the site of C–H oxidation based on both stereoelectronic factors and also conformational control. We are currently exploring the synthesis of 3-amino-sugars, especially those that contain a quaternary centre such as vancosamine, for which this reaction might see potential direct application.

Acknowledgements

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Notes and references

‡ The sample of **1** was mounted in perfluorinated polyether oil on a hair and quench-cooled to 150 K using an Oxford Cryosystems Cryostream 600 series open-flow N_2 cooling device.[16] Data were collected using a Nonius Kappa-CCD area detector diffractometer, with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Cell parameters and intensity data were processed using the DENZO-SMN package and reflection intensities were corrected for absorption effects by the multi-scan method, based on multiple scans of identical and Laue equivalent reflections.[17] The structure was solved by direct methods using SIR92[18] and refined by full-matrix least squares on F^2 using the CRYSTALS suite.[19] All non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were generally visible in the difference map, but were positioned geometrically and refined separately with soft restraints before inclusion in the final refinements using a riding model.[20] The Flack *x* parameter[21] refined to −0.02(4) and analysis of the Bijvoet pairs to gave a Hooft *y* parameter of 0.00(2) giving a < 0.00001% probability that the structure is the incorrect hand (assuming enantiopurity or racemic twinning).[22] **Crystal data** (clear yellow plate, 0.03 × 0.10 × 0.14 mm): $C_9H_{15}NO_7S$ M_r = 281.29; Triclinic, *P*1; *a* = 6.0756(2) Å, *b* = 6.6423(2) Å, *c* = 7.3505(2) Å, α = 80.5318(12)°, β = 84.2434(12)°, γ = 89.0269(12)°, *V* = 291.120(15) Å^3; *T* = 150 K; *Z* = 2; μ = 0.306 mm^{-1}; D_c = 1.604 gcm^{-3}; $\Delta\rho_{min,max}$ = −0.24,0.20 *e* A^{-3}. Reflections collected = 6964; independent reflections = 2545 (R_{int} = 0.034); *R* indices [$I > 3\sigma(I)$, 2498 reflections]: R_1 = 0.0232, wR_2 = 0.0567. CCDC 776943.

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