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Protecting Group and Solvent Control of Stereo- and Chemoselectivity in Glucal 3-Carbamate Amidoglycosylation

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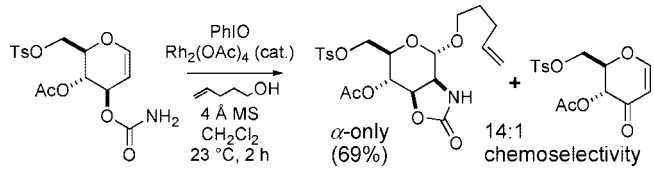
ABSTRACT



In the $Rh_2(OAc)_4$-catalyzed amidoglycosylation of glucal 3-carbamates, anomeric stereoselectivity and the extent of competing C3−H oxidation depend on the 4*O* and 6*O* protecting groups. Acyclic protection permits high α-anomer selectivity with further improvement in less polar solvents, while electron-withdrawing protecting groups limit C3-oxidized byproducts. Stereocontrol and bifurcation between alkene insertion and C3−H oxidation reflect an interplay of conformational, stereoelectronic, and inductive factors.

2-Amino sugars having a 2,3-cis stereo array include *N*-acetylmannosamine (ManNAc, **1**), which is the biosynthetic precursor of the sialic acids,[1] and 2-allosamine, a constituent of the potent Chitinase inhibitor allosamidin (**2**)[2] and a useful ligand scaffold (**3**)[3] for asymmetric catalysis. The challenge of stereoselective C2−N bond construction is acute in these systems, and control of anomeric configuration in the preparation of glycoside derivatives is desirable. Synthetic methods based on intermolecular additions to glycals typically place the C2−N group trans to the C3-oxygen substituent.[4] Gin's activated-sulfoxide-mediated acetamidoglycosylation[5] of glucals is an exception, producing ManNAc structures, though with *N*-acetylglucosamine (GlcNAc) byproducts.[5c]

As an alternative,[6] we have used intramolecular nitrogen atom delivery from allal 3-azidoformates,[7] allal 3-carbamates,[8] and glucal 3-carbamates[9] to establish the 2,3-cis relationship. With the 3*O*-carbamoyl glycals, we extended Du Bois's C−H amidation method[10] to alkene insertion,[11,12] a new reaction of allylic carbamates.[13] Mechanistic studies[14] imply that these conditions produce rhodium nitrenoids having reactivity strikingly analogous to metal carbenoids.[15] With iodosobenzene (PhIO)[16] instead of $PhI(OAc)_2$ as the oxidant, we achieved in situ glycosylation of alcohols without nucleo-

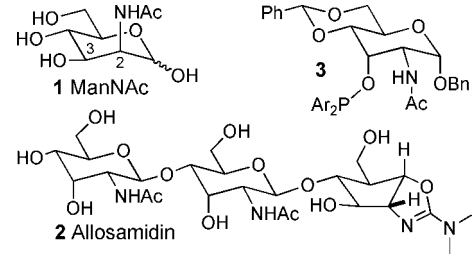


Figure 1. 2-Amino sugars with cis-2,3 stereochemistry.

[†] Columbia University NMR Laboratory.

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philic competition from acetate, an overall amidoglycosylation process.[8,9,17]

Allal frameworks (e.g., **4**, Scheme 1) provided high 1,2-trans selectivity, offering a concise route to β-linked 2-amidoallopyranosides as found in allosamidin.[7,8] However, in the C3-epimeric series, our one-pot amidoglycosylation process applied to glucal 3-carbamates **6a** and **6b**, having 4*O*,6*O* acetonide or di-*tert*-butylsilylene protection, gave anomeric mixtures only slighly favoring the 1,2-trans products **7-α** and also generated dihydropyranone byproducts **8a** and **8b** via oxidation at the C3−H bond (Table 1, entries 1 and 5).[9] Using 4-penten-1-ol as the acceptor, we were able to stereoconvergently advance either anomer of *n*-pentenyl glycoside[18] **7a**, but the lack of amidoglycosylation selectivity stymied direct access to α-linked ManNAc derivatives.[9]

Scheme 1. β-Selective Allal 3-Carbamate Amidoglycosylation

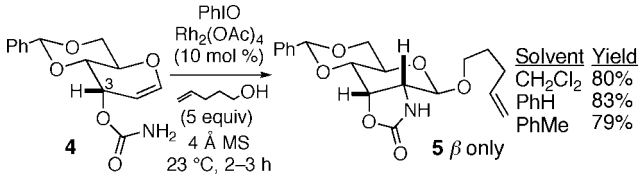
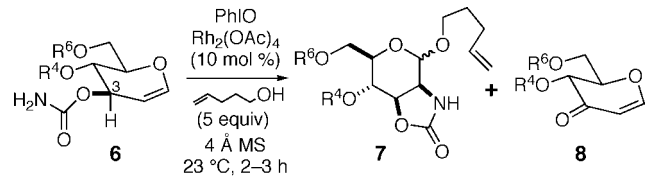


Table 1. Protecting Group and Solvent Effects on Stereo- and Chemoselectivity of Glucal 3-Carbamate Amidoglycosylation



entry	R^6	R^4	**6**	$J_{H4,H5}$ in **6**[a]	rxn solvent	**7**:**8**[b] (%**7**-**α**)[c]	α:β[b] **7**
1[d]	-CMe_2-		**a**	9.9[e]	CH_2Cl_2	3.1:1(40)	1.3:1
2			**a**		PhH	4.3:1(32[f])	1.3:1
3			**a**		Hex/PhH 5/1	4.9:1(38[f])	2.4:1
4			**a**		Hex/PhH 10/1	4.7:1(34)	2.7:1
5[d]	-Si^tBu_2-		**b**	10.0	CH_2Cl_2	3.2:1 (33)	2.2:1
6			**b**		PhH	3.5:1 (29)	1.7:1
7			**b**		Hex	3.7:1 (43)	3.6:1
8	Bn	Bn	**c**	8.8	CH_2Cl_2	2.9:1 (61)	12:1
9			**c**		PhH	2.3:1 (47)	α only
10			**c**		CH_2Cl_2/ Hex 1/1	3.0:1 (54)	22:1
11			**c**		CH_2Cl_2/ PhH 1/1	3.0:1 (56)	23:1
12	Ac	Ac	**d**	7.5	CH_2Cl_2	15:1 (69)	α only
13	Ts	Ac	**e**	6.7[g]	CH_2Cl_2	14:1 (69)	α only
14	-CO-		**f**	10.4[h]	CH_2Cl_2	2.4:1 (32)	2.9:1
15	TBS	Ac	**g**	7.9	CH_2Cl_2	6.6:1 (68)	25:1
16	Ts	TBS	**h**	9.0	CH_2Cl_2	8.1:1 (67)	12:1
17	TBS	TBS	**i**	9.4	CH_2Cl_2	2.4:1 (46[i])	5.8:1

[a] In Hz, $CDCl_3$ unless otherwise noted. [b] From ^1H and ^{13}C NMR of the crude reaction mixture. [c] Isolated yield of the α anomer. [d] Data from ref 9. [e] In DMSO-d_6. [f] NMR yield of the α anomer vs mesitylene as an internal standard. [g] In C_6D_6. [h] In acetone-d_6. [i] Calcd from the total yield (54%) of inseparable anomeric mixture.

Herein we report that proper choice of 4*O* and 6*O* protecting groups and solvent enables high levels of stereocontrol and chemoselectivity in amidoglycosylation of glucal 3-carbamates. Our studies also illuminate electronic and conformational aspects of both amidoglycosylation and the competing C3−H oxidation.

For comparison, we began by treating benzylidene-protected allal 3-carbamate **4**[8] under our standard conditions with 4-penten-1-ol as the acceptor (Scheme 1). As in our previous study with other acceptors,[8] only β product **5**, unaccompanied by dihydropyranone, was observed. The outcome was comparable in the three solvents tested.

By analogy with our earlier results[7,8] and Padwa's studies,[11] we attribute high 1,2-trans selectivity to nucleophilic opening of a glycosyl aziridine.[4c,17,19] In the glucal series, low anomeric stereocontrol might be due to glycosylation via an oxocarbenium intermediate. Padwa has invoked aziridine-opened zwitterions in reactions of indolyl and benzofuranyl carbamates.[11]

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We evaluated the effect of solvent polarity on anomeric stereoselectivity, beginning with acetonide- and di-*tert*-butylsilylene-protected glucal 3-carbamates **6a** and **6b** (Table 1, entries 1−7). There was a modest trend toward higher α selectivity in less polar solvents, which we reasoned favored assistance from the C2 nitrogen versus an oxocarbenium donor. However, with the cyclic 4*O*,6*O* protection in **6a** and **6b**, maintaining N-anomeric contact in the donor entails significant strain.

To better enable an α-selective aziridine donor (**C**, Figure 2), we removed the stricture of cyclic 4*O*,6*O* protection. Dibenzyl-protected **6c**[20] provided high to complete α selectivity, depending on solvent (Table 1, entries 8−11). In benzene, we detected only the α anomer, but the yield was lowered and we noted chloroform-insoluble material in the crude product that was not present when the reaction solvent was CH_2Cl_2. Mixed solvents with a less polar component increased α selectivity while better maintaining yields relative to CH_2Cl_2 alone.

Unfortunately, the dibenzyl protection in **6c** did not remedy the chemoselectivity problem. Our mechanistic model (Figure 2) is that amidoglycosylation and C3 oxidation both occur via rhodium nitrenoid conformers **A**/**A′**. Du Bois has reported

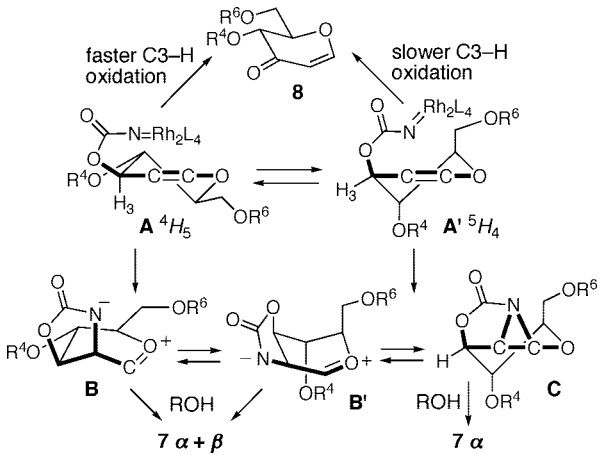

Figure 2. Model for factors affecting anomeric stereoselectivity and extent of C3−H oxidation.

ketone formation in reactions of secondary-alcohol-derived carbamates and tentatively ascribed them to C−H insertion at the α position, followed by fragmentation of the resulting four-membered-ring carbamate.[21] In the carbenoid field, Doyle found that the diazoacetate ester of 1-indanol provides 1-indanone and ketene upon treatment with dirhodium(II) catalysts.[22] The proposed mechanism involves intramolecular hydride transfer to the rhodium acyl carbenoid.[22,23] Another possible path to byproduct **8**, involving initial reaction of the enol ether π bond with the hypervalent iodine oxidant, is not consistent with our control experiments.[24]

The extent of the unwanted oxidation should depend on the electronic characteristics of the C3−H bond. As was found with rhodium carbenoids,[25] C−H insertion of rhodium nitrenoids is most favorable for electron-rich C−H bonds.[14] Insertion α to oxygen is facile,[26] and Parker's group has described activation of allylic C−H bonds vinylogously α to the ring oxygen of glycal substrates.[27] Compain suggested that an anomeric C−H bond is more reactive toward nitrenoid insertion in an axial rather than equatorial position,[28] an effect recognized in carbenoid reactions.[29] In our glucal 3-carbamate systems, a vinylogous anomeric effect[30] may activate the pseudoaxial C3−H bond for insertion (**A**→**8**). By contrast, in allal 3-carbamate **4** (Scheme 1) or in glucal conformer **A′** the C3−H bond has the pseudoequatorial orientation.

Our analysis prompted two substrate-controlled[31] approaches for minimizing C3−H oxidation. First, electron-withdrawing 4*O* and 6*O* protecting groups might inductively deactivate the C3−H bond toward nitrenoid insertion. Second, shifting the conformational equilibrium from all-equatorial $^4H_5$ (**A**) toward inverted $^5H_4$ (**A′**) would diminish stereoelectronic priming of the C3−H bond. The conformational preference in glucals is sensitive to hydroxyl protection,[32] and the $^4H_5$/$^5H_4$ distribution can affect the stereoselectivity of addition reactions at the glycal alkene.[32b] Electron-withdrawing substituents at C6, including Br and OTs, along with 3*O*-ester protection, favor the inverted $^5H_4$ conformation.[32] This raised the possibility of simultaneous inductive and conformational deactivation of the C3−H bond, diminishing the formation of byproduct **8**. These effects could also improve stereocontrol by stabilizing aziridine donor **C** relative to **B**/**B′** (half-chair conformers lacking the stereocontrolling element of covalent[33] N−C1 attachment) and by

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(20) See Supporting Information for carbamate syntheses.

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(24) No reaction of **6b** occurred in the absence of Rh(II) catalyst, and non-redox-active Lewis acid catalysts $Sm(OTf)_3$, $Ln(OTf)_3$, or $Zn(OTf)_2$ did not produce byproduct **8b** (or any **7b**) from **6b**. We also noted earlier (ref 8) that tri-*O*-acetyl-D-glucal does not react under our conditions, though it is a substrate for Kirschning-type oxidation: (a) Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267–2274. Compare: (b) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 5039–5042.

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(31) An alternative would be catalyst-controlled chemoselectivity. In our systems, of various Rh(II) carboxylates examined, only $Rh_2(OAc)_4$ and Du Bois's $Rh_2(esp)_2$ provided complete conversion, and neither catalyst was satisfactory in limiting C3-H oxidation. Catalyst control of chemoselectivity in rhodium nitrenoid and carbenoid insertions, respectively: (a) Hayes, C. J.; Beavis, P. W.; Humphries, L. A. *Chem. Commun.* **2006**, 4501–4502. (b) Davies, H. M. L.; Coleman, M. G.; Ventura, D. L. *Org. Lett.* **2007**, *9*, 4971–4974.

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favoring the conformation required for forming the aziridine directly (**A′**→**C**) without intervention of zwitterion **B/B′**.

To probe these influences, we synthesized a range of glucal 3-carbamates **6d**-**i**[20] for comparison with **6a**-**c**. Analysis of the crude reaction mixtures by ^{1}H and ^{13}C NMR determined anomeric stereoselectivity in products **7** and the proportion of byproducts **8** (see Table 1).[34] To estimate conformational effects on the reactivity of the derived rhodium nitrenoids (**A**/**A′**), we determined $J_{H4,H5}$ for each glucal 3-carbamate **6**. In various instances, second-order behavior in the ^{1}H NMR spectra (up to 500 MHz) required coupled HSQC techniques for determining $J_{H4,H5}$.[35] Decreasing values of $J_{H4,H5}$ indicate an increasing proportion of conformationally inverted **A′**, having the equatorial-equatorial H4−H5 relationship.[32]

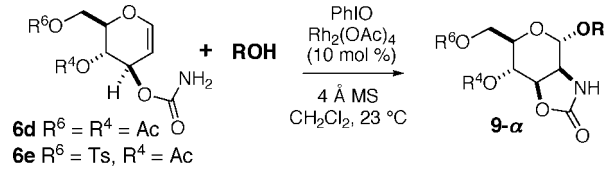
With 4,6-di-*O*-acetyl-protected **6d** and 4-*O*-acetyl-6-*O*-tosyl derivative **6e** (Table 1, entries 12 and 13), much less of the C3−H-oxidized byproducts formed, compared to dibenzyl-protected **6c**. In addition, we detected only the α anomers of **7d** and **7e** from reactions in CH_2Cl_2. From the $J_{H4,H5}$ values, **6d** and **6e** are both weighted more toward the $^5H_4$ conformation than the dibenzyl-protected **6c**.

To better understand conformational and inductive contributions to stereo- and chemoselectivity, we used **6f**, having the cyclic-carbonate-locked $^4H_5$ conformation (Table 1, entry 14). Despite the electron-withdrawing character of the 4,6-*O*-carbonate protection, **6f** led to considerable byproduct **8f** and a mixture of anomers, supporting conformational flexibility as a requirement for high chemo- and stereoselection.

Just one electron-withdrawing group at either 4*O* or 6*O*, as in **6g** and **6h** (Table 1, entries 15 and 16), gave better chemoselectivity than either the dibenzyl- or the disilyl-protected carbamates **6c** or **6i** (cf. entries 8 and 17). The 4*O*-acetyl group in **6g** engendered a higher $^5H_4$ proportion and excellent anomeric selectivity, but was comparable to the 6*O*-tosyl of **6h** in enforcing chemoselection.[36] The large silyl groups in **6i** (Table 1, entry 17) led to decreased anomeric selectivity relative to the dibenzyl-protected **6c**.

Using stereo- and chemoselective substrates **6d** and **6e**, we have begun studying reactions with various acceptor alcohols (Table 2). Reducing the amount of acceptor posed a challenge since reactions became sluggish and yields were lower (cf. entries 1 and 2). Reasoning that excess alcohol might be needed to activate CH_2Cl_2-insoluble iodosobenzene,[37] we tested hexafluoroisopropanol (HFIP), a useful solvent in reactions of hypervalent iodine oxidants,[38] as an additive (entries 3 and 8). Although yields did not improve much, consumption of starting material was considerably faster with HFIP added, and the weakly nucleophilic additive did not compete as the acceptor. Increasing the concentration of substrate **6** was also helpful, although 0.2 M is close to the upper limit for this initially heterogeneous reaction.

Table 2. Amidoglycosylation with Various Acceptor Alcohols



6d R^6 = R^4 = Ac
6e R^6 = Ts, R^4 = Ac

entry	6	[6] (M)	ROH (equiv)	equiv HFIP[a]	9-α (%)[b]	α:β[c]
1	**6d**	0.090	**a** (5.0)	none	**9da** (58)	>20:1
2	**6d**	0.090	**a** (2.0)	none	**9da** (40)	12:1
3	**6d**	0.091	**a** (2.0)	3.0	**9da** (41)	7.1:1
4	**6d**	0.21	**a** (2.0)	none	**9da** (47)	13:1
5	**6e**	0.089	**b** (5.0)	none	**9eb** (51)	12:1
6	**6e**	0.19	**b** (2.1)	none	**9eb** (40)	9.3:1
7[d]	**6e**	0.19	**c** (2.0)	none	**9ec** (41)	-*e*-
8	**6e**	0.19	**c** (2.0)	1.0	**9ec** (44)	-*e*-

[a] 1,1,1,3,3,3-Hexafluoroisopropanol. [b] Isolated yield of the α anomer, corrected in entries 1−6 for small amounts of chromatographically inseparable C1−C2 oxidative cleavage byproduct (see Supporting Information for details). [c] From ^{1}H NMR of the crude reaction mixture. [d] Starting carbamate **6e** (15%) remained. [e] β Anomer was not detected.

Stereo- and chemoselectivity in the amidoglycosylation of glucal 3-carbamates reflects a confluence of inductive, conformational, and stereoelectronic effects. Acyclic 4*O*,6*O* protection enables high anomeric stereocontrol. Electron-withdrawing, $^5H_4$-favoring 4*O* and 6*O* groups suppress C3−H oxidation and further enhance stereoselectivity. The net result is direct access to variably protected 2*N*,3*O* mannosamine oxazolidinones from glucal 3-carbamates. Studies with other glycal stereoisomers and optimization with a range of acceptors are underway.

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Supporting Information Available: Experimental details and compound characterization, including preparation of carbamates **6**, determination of $J_{H3,H4}$ values, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) Since dihydropyranones **8** are Michael acceptors for alcohols under basic or acidic conditions (for example: Mann, B.; Pitts, D.; Koviach, J. *J. Carbohydr. Chem* **2005**, *24*, 161–168.), we verified their stability under the reaction conditions. See Supporting Information for details.

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