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Nickel-Catalyzed Stereoselective Formation of α-2-Deoxy-2-Amino Glycosides

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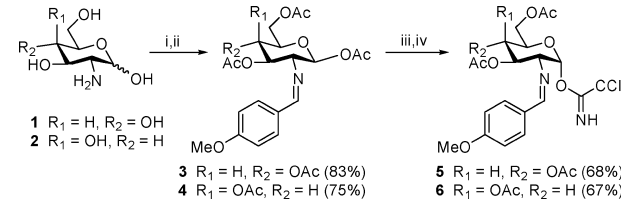
The α-2-deoxy-2-amino glucosides and galactosides are the structural units found within a variety of biologically important glycoconjugates.[1−5] The stereoselective synthesis of α-1,2-cis-glycosides of D-glucosamine and D-galactosamine is challenging because it requires a nonassisting neighboring group effect at the C(2)-amino functionality on the glycosyl donor to direct the α-selectivity.[6] Early work in this area employs the C(2)-azide functionality on the glycosyl donor as a nonparticipatory group.[7] However, the stereochemical outcome can be difficult to predict and often resulted in moderate α-selectivity.[4b] In 2001, Kerns reported an elegant strategy utilizing a glycosyl donor incorporated with the C(2)-oxazolidinone group.[8a] This approach requires 2 equiv of the activating reagent (PhSOTf), and undesired *N*-glycosylation[8b] and sulfenylation[8a] are also observed in the reaction. Later, Schmidt reported the conjugate addition of alcohols to C(2)-nitro-galactals in the presence of *t*-BuOK to afford α-2-deoxy-2-nitro-galactosides in good yields.[9] Gin has recently reported the opening of aziridine with C(1)-hemiacetal nucleophiles to form α-*O*-glycosyl serine conjugates in good diastereoselectivity.[10] Despite the variety of methods available, selective synthesis of α-2-dexoy-2-amino glycosides continues to be a challenge because each of the above methodologies has its own advantages and disadvantages.

The use of *para*-methoxybenzylidene as the protecting group for the C(2)-nitrogen on glycosyl bromide was investigated over 40 years ago.[11] However, its use was complicated due to the low stability of the Schiff base as well as the multistep synthesis required for the preparation of glycosyl bromide. Additionally, the stereochemical outcome of the coupling process depends on the nature of the promoters as well as the alcohol acceptors. For instance, utilizing stoichiometric amounts of HgCN provides the desired glucosides selectively either as the α-isomers[12] or as the β-isomers[13] depending on the nature of the alcohol acceptors. In contrast, the use of AgOTf (2 equiv) as a promoter provides glucosides exclusively as β-isomers.[13] On the other hand, the *n*-pentenyl glycoside approach provides α-glucoside in moderate yield.[14] In this communication, we report the use of C(2)-*para*-methoxybenzylideneamino trichloroacetimidates **5** and **6** as the donors (Scheme 1) for the stereoselective synthesis of α-2-deoxy-2-amino glycosides. This strategy relies on the nature of the ligand on nickel to control the α-selectivity. This method requires only a catalytic amount of the cationic nickel catalyst to activate trichloroacetimidate donors at ambient temperature. Furthermore, its application is widespread to a variety of alcohol nucleophiles.

The straightforward synthesis of **5** and **6** commenced with D-glucosamine (**1**) and D-galactosamine (**2**), respectively. Exposure of **1** and **2** to *p*-anisaldehyde and NaOH followed by acetylation provided **3** and **4** in good yields (Scheme 1).[15] Chemoselective 1-*O*-deacetylation with NH_3 in MeOH and subsequent treatment of the resulting hemiacetals with trichloroacetonitrile in the presence of DBU afforded trichloroacetimidates **5** and **6**. With these donors in hand, our attention was focused on the glycosylation reactions.

Initial experiments were performed with trichloroacetimidate **5** as the donor and primary alcohol of galactoside **7** as the acceptor (Table 1). Upon treatment of both coupling partners **5** and **7** with 5 mol % of

Scheme 1[a]

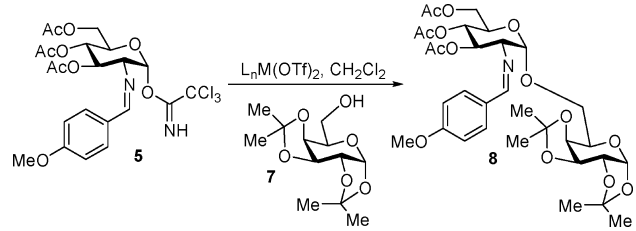


[a] (i) *p*-Anisaldehyde, NaOH (1 M); (ii) Ac_2O, DMAP, pyridine; (iii) NH_3 in MeOH, THF; (iv) Cl_3C-CN, DBU, CH_2Cl_2.

cationic $Pd(PhCN)_2(OTf)_2$,[16] the reaction proceeded sluggishly at 0 °C to give the desired disaccharide **8** in poor yield with moderate diastereoselectivity (entry 1). Warming the reaction to 25 °C shortened the reaction time and increased the yield (entry 2). Switching to the cationic nickel catalyst improved the yield and the α-selectivity, and **8** was isolated in 95% yield with $\alpha:\beta = 8:1$ (entry 4).[17] We then investigated the nature of the ligands on nickel to influence the anomeric selectivity. The more electron-withdrawing substituted benzonitrile ligands decreased the reaction time and increased the α-selectivity (entries 5 and 6). On the other hand, the more electron-rich ligands increased the reaction time (entries 7 and 8). These results clearly demonstrate the efficiency of the nickel method, with the formation of disaccharide **8** with excellent α-diastereoselectivity. It has been reported that coupling of the C(2)-azide donor derivative of **5** with **7** provided a 2:1 mixture of α- and β-isomers.[18]

Glycosylation of alcohol acceptor **9** with **5** has been attempted under Lewis acid conditions.[13] The reaction did not occur in the presence of TMSOTf as a promoter, and the use of $BF_3 \cdot OEt_2$ resulted in only a trace amount of the desired disaccharide **10**. Encouraged by the results

Table 1. Selective Formation of α-Disaccharide **8**[a]



entry	catalyst	loading	temp	time	yield[b]	α:β[c]
1	$Pd(PhCN)_2(OTf)_2$	5 mol %	0 °C	15 h	41%	5:1
2	$Pd(PhCN)_2(OTf)_2$	5 mol %	25 °C	6 h	60%	4:1
3	$Pd(PhCN)_2(OTf)_2$	7 mol %	25 °C	4 h	63%	5:1
4	$Ni(PhCN)_4(OTf)_2$	5 mol %	25 °C	4 h	95%	8:1
5	$Ni(4\text{-}CF_3\text{-}PhCN)_4(OTf)_2$	5 mol %	25 °C	3 h	90%	10:1
6	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5 mol %	25 °C	3 h	93%	10:1
7	$Ni(4\text{-}MeOPhCN)_4(OTf)_2$	5 mol %	25 °C	6 h	76%	10:1
8	$Ni(dppe)(OTf)_2$	5 mol %	25 °C	7 h	95%	8:1

[a] The reactions were performed with 5−7 mol % of $Pd(PhCN)_2(OTf)_2$ or 5 mol % of $L_nNi(OTf)_2$ which was generated in situ from L_nNiCl_2 and AgOTf. [b] Isolated yield. [c] ^1H NMR ratio.

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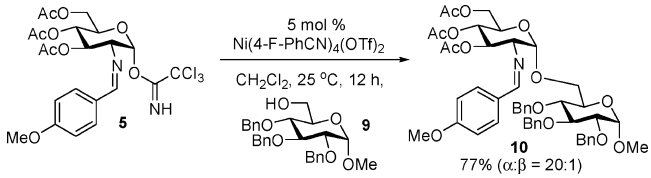
obtained in Table 1, we decided to explore the feasibility of the cationic nickel method with both coupling partners **5** and **9** (Scheme 2). The reaction proceeded smoothly to provide disaccharide **10** in 77% yield with excellent diastereoselectivity (α:β = 20:1). Compared to other glycosylation methods,[13,19] this chemistry is more α-selective. For instance, coupling of **9** with glycosyl bromide derivative of **5** in the presence of AgOTf (1.5 equiv) as a promoter provided the β-isomer of **10** as the major product (α:β = 1:9).[13] On the other hand, glycosylation of **9** with C(2)-oxazolidinone thioglycoside donor afforded glycoconjugate in 81% yield with α:β = 3:1.[19]

Scheme 2

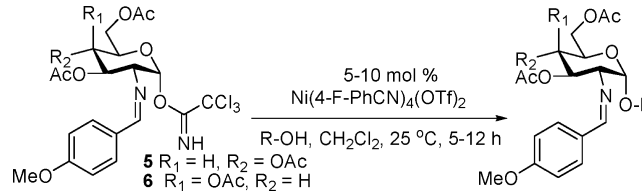


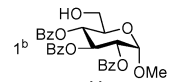
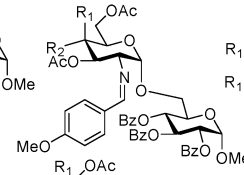
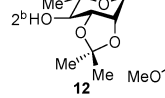
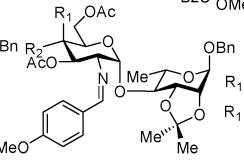
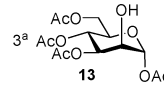
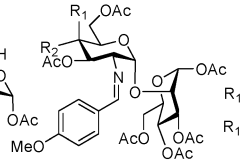
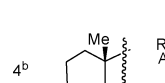
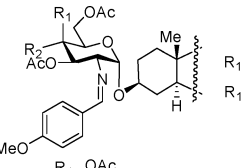
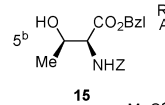
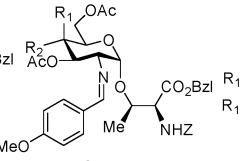
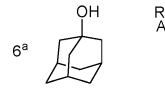
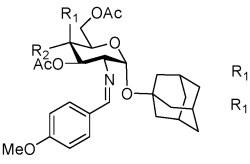
The scope of this new coupling method was further examined with a number of primary, secondary, and tertiary alcohols **11**−**16** (Table 2). The desired glucosides **17**−**22** were isolated in good yields with excellent α-selectivity (entries 1−6). For instance, glycosylation of primary alcohol **11** with C(2)-benzylideneamino donor **5** under nickel-catalyzed conditions provided disaccharide **17** in 78% yield with α:β = 15:1 (entry 1). On the other hand, coupling of **11** with the C(2)-azide derivative of **5** yielded a 8:1 mixture of α- and β-isomers.[18] In the case of glycosyl acceptor **13**, the nickel-catalyzed glycosylation reaction provided disaccharide **19** in 97% yield exclusively as α-isomer (entry 3). Under the Kochetkov's C(2)-azide thiocyanate donor, glycosylation of **13** also afforded exclusively the α-coupling product, albeit in lower yield (72%).[20] With use of dihydrocholesterol **14** as a nucleophile, the glycoconjugate **20** was obtained in 85% yield with α:β = 11:1 (entry 4). Under the Oscarson's oxazolidinone conditions, the coupling product was obtained exclusively as the β-isomer when dihydrochlolesterol was employed as a glycosyl acceptor.[21] The α-isomer, however, could be obtained when a significant amount of AgOTf (0.4 equiv) was employed in the reaction.[21] Under nickel-catalyzed conditions, coupling of L-threonine **15** with **5** provided glycopeptide **21** with α:β =10:1 (entry 5). In contrast, a 2.5:1 mixture of α- and β-isomers was obtained when C(2)-azide donor was employed in the coupling process.[22] Overall, the nickel-catalyzed glycosylation with C(2)-benzylideneamino glycosyl donor **5** provided a practical approach to get access to a variety of glycoconjugates with high α-selectivity. Additionally, it does not require PhSEt as a putative nucleophile (the azide method)[18] or a large quantity of AgOTf (the oxazolidinone method)[21] to improve the α-selectivity. It only requires a catalytic amount of cationic nickel catalyst (5−10 mol %) to activate glycosyl donor **5**, leading to the formation of the coupling products with excellent α-selectivity.

Similarly, D-galactosamine substrate **6** was found to be a viable donor, and glycoconjugates **23**−**28** were obtained with excellent α-selectivity. Notably, the efficiency of the reaction is illustrated by the ability to provide *O*-threonine conjugate **27** in 74% yield with α:β = 14:1 (entry 5). Under the oxazolidinone method, coupling of threonine afforded glycopeptide as a 1:1 mixture of α- and β-isomers.[8] On the other hand, the C(2)-azide glycosyl bromide donor provided glycopeptide in 60% yield with α:β = 4:1.[23]

The efficacy of this nickel-catalyzed α-glycosylation was further explored with other *N*-substituted benzylidene derivatives on trichloroacetimidate donors (Table 3). Coupling of **7** with the C(2)-benzylideneamino donor provided disaccharide **29** in 92% yield with α:β = 10:1 (entry 1). On the other hand, switching to the electron-withdrawing *N*-substituted benzylidenes shortened the reaction time from 3 to 1 h, and the coupling products **30** and **31** were still obtained with similar yields and α-selectivity (entries 2 and 3).

Table 2. Substrate Scope



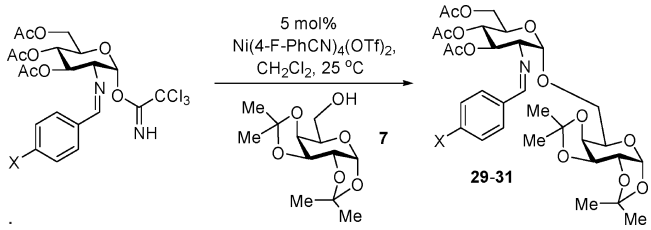
Entry	R-OH	Products		Yield[d]	α:β[e]
1[b]			R_1 = H, R_2 = OAc **17**	78%	15:1
			R_1 = OAc, R_2 = H **23**	72%	14:1
2[b]			R_1 = H, R_2 = OAc **18**	93%	12:1
			R_1 = OAc, R_2 = H **24**	80%	12:1
3[a]			R_1 = H, R_2 = OAc **19**	97%	α only
			R_1 = OAc, R_2 = H **25**	93%	α only
4[b]			R_1 = H, R_2 = OAc **20**	85%	11:1
			R_1 = OAc, R_2 = H **26**	80%	10:1
5[b]			R_1 = H, R_2 = OAc **21**	73%	10:1
			R_1 = OAc, R_2 = H **27**	74%	14:1
6[a]			R_1 = H, R_2 = OAc **22**	96%	17:1
			R_1 = OAc, R_2 = H **28**	84%	12:1

[a] 5 mol % of Ni(II) catalyst was employed. [b] 10 mol % of Ni (II) catalyst was employed. [c] Dihydrocholesterol. [d] Isolated yield. [e] ^{1}H NMR ratio.

A possible mechanism for the cationic nickel-catalyzed reaction reported herein is shown in Scheme 3. Reversible coordination of $L_nNi(OTf)_2$ to both C(1)-trichloroacetimidate nitrogen and C(2)-benzylidene imine of donor **32** forms a seven-membered ring complex **33**. It is hypothesized that hydrogen bonding between the external oxygen nucleophile and trichloroacetamide facilitates ionization of species **33** to produce complex **34**. Subsequent ligand exchange followed by dissociation of trichloroacetamide provides ion-pair **35**. The intermediate **35** then recombines in a stereoelectronically favored mode to form a five-membered ring complex **36**. Dissociation of the nickel catalyst from complex **36** yields α-product **37**.

To verify that the presence of the external oxygen nucleophile is necessary for the facile ionization of a seven-membered ring complex

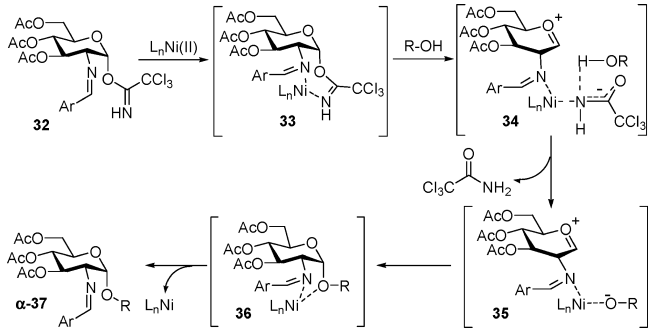
Table 3. Other *N*-Substituted Benzylidene Derivatives[a]



entry	X	time	disaccharide	yield[b]	α:β[c]
1	H	3 h	**29**	92%	10:1
2	CF_3	1 h	**30**	87%	9:1
3	F	1 h	**31**	96%	9:1

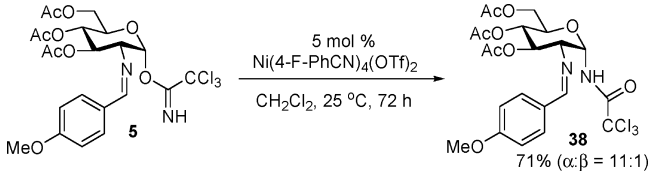
[a] The reactions were performed with 5 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ in CH_2Cl_2 (0.2 M). [b] Isolated yield. [c] ^{1}H NMR ratio.

Scheme 3



such as **33** (Scheme 3), a control experiment was attempted in the absence of a nucleophilic acceptor (Scheme 4). The rearrangement of **5** was sluggish, and it took 72 h for the reaction to go to completion. The desired trichloroacetamide **38** was obtained in 71% with excellent α-selectivity (α:β = 11:1).

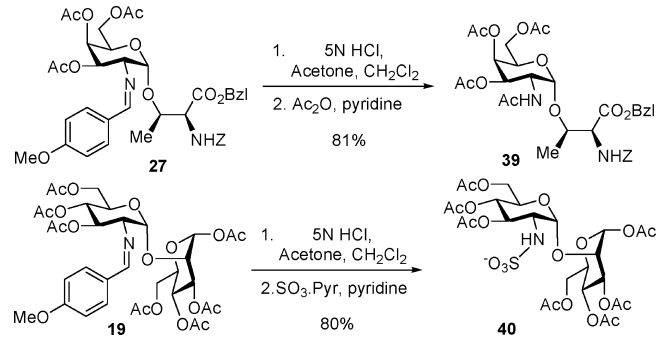
Scheme 4



To illustrate the potential utility of glycoconjugate products, the following transformations were performed. Removal of the *para*-methoxylbenzylidene following acetylation and sulfation furnished **39** and **40** (Scheme 5). The glycoconjugate **39** is a fully protected structure of a T_N-tumor associated antigen.[4] Compound **40** is a structural analogue of heparin derivatives.[1]

In summary, a general and practical method for stereoselective synthesis of α-2-deoxy-2-amino glycosides has been developed. The C(2)-benzylideneamino trichloroacetimidate donors can be easily prepared in four steps starting from commercially available D-glucosamine and D-galactosamine. These glycosyl donors are able to couple to primary, secondary, and tertiary alcohols to provide access to a variety of glycoconjugates with excellent α-selectivity. The diastereoselectivity of the current nickel-catalyzed reaction depends on the nature of the cationic nickel catalyst. The reactive sites of the nucleophilic acceptors or the nature of the protecting groups have little effect on the α-selectivity. Additionally, only a catalytic amount of nickel is required for the coupling reaction to occur at room temperature. Mechanistic studies of the present reaction are currently underway and will be reported in due course.

Scheme 5



Acknowledgment. This work is dedicated to Professor Paul Grieco on the occasion of his 65th birthday and with gratitude for his mentorship. We thank Montana State University for financial support and Ms. Shannon Atkins for the generous gift of **13**.

Supporting Information Available: Experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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