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Nickel-Catalyzed Stereoselective Glycosylation with C(2)-*N*-Substituted Benzylidene D-Glucosamine and Galactosamine Trichloroacetimidates for the Formation of 1,2-*cis*-2-Amino Glycosides. Applications to the Synthesis of Heparin Disaccharides, GPI Anchor Pseudodisaccharides, and α-GalNAc

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Abstract: The 1,2-*cis*-2-amino glycosides are key components found within a variety of biologically important oligosaccharides and glycopeptides. Although there are remarkable advances in the synthesis of 1,2-*cis*-2-amino glycosides, disadvantages of the current state-of-the-art methods include limited substrate scope, low yields, long reaction times, and anomeric mixtures. We have developed a novel method for the synthesis of 1,2-*cis*-2-amino glycosides via nickel-catalyzed α-selective glycosylation with C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidates. These glycosyl donors are capable of coupling to a wide variety of alcohols to provide glycoconjugates in high yields with excellent levels of α-selectivity. Additionally, only a substoichiometric amount of nickel (5−10 mol %) is required for the reaction to occur at 25 °C. The current nickel method relies on the nature of the nickel−ligand complex to control the α-selectivity. The reactive sites of the nucleophiles or the nature of the protecting groups have little effect on the α-selectivity. This methodology has also been successfully applied to both disaccharide donors and acceptors to provide the corresponding oligosaccharides in high yields and α-selectivity. The efficacy of the nickel procedure has been further applied toward the preparation of heparin disaccharides, GPI anchor pseudodisaccharides, and α-GluNAc/GalNAc. Mechanistic studies suggest that the presence of the substituted benzylidene functionality at the C(2)-amino position of glycosyl donors is crucial for the high α-selectivity observed in the coupling products. Additionally, the α-orientation of the C(1)-trichloroacetimidate group on glycosyl donors is necessary for the coupling process to occur.

Introduction

The C(2)-aminoglycosides are key components in glycoproteins, one of the most important classes of naturally occurring oligosaccharides and glycoconjugates.[1] Over half of biologically important proteins are glycosylated in the form of glycoproteins. Many of these aminosugars are found on cell surfaces and play a crucial role as receptor ligands for macromolecules such as lectins, antibodies, and enzymes.[2] They also participate in antibody−antigen interactions. Glycosides of 2-aminosugars are linked to other sugar residues or serine/threonine amino acids via either 1,2-*cis*- or 1,2-*trans*-2-amino *O*-glycosidic bonds (Figure 1).

The synthesis of 1,2-*trans*-2-amino glycosides can be accomplished by employing donors with C(2)-participatory protecting groups. In contrast, despite the variety of methods available, the stereoselective construction of 1,2-*cis*-2-amino glycosides remains challenging because it requires donors with nonassisting neighboring groups at the C(2)-amino position. The most commonly used method employs glycosyl donors with a C(2)-azido functionality as the nonparticipatory group.[3] Under the C(2)-azido method, the anomeric selectivity at the newly formed glycosidic bond can be difficult to predict, forming mixtures of α- and β-isomers.[4] In response to this problem, Kerns reported an elegant strategy utilizing glycosyl donors containing an oxazolidinone group spanning the C(2)- and C(3)-positions.[5] This approach requires at least 2 equiv of the

(1) (a) Petitou, M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3118–3133. (b) Echardt, K. *J. Nat. Prod.* **1983**, *46*, 544–550. (c) Magnet, S.; Blanchard, J. S. *Chem. Rev.* **2005**, *105*, 477–497. (d) Danishefsky, S. J.; Allen, J. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 836–837. (e) Marcaurelle, L. A.; Bertozzi, C. R. *Glycobiology* **2002**, *12*, 69R–77R. (f) Ferguson, M. A. J.; Williams, A. F. *Annu. Rev. Biochem.* **1988**, *57*, 285–320. (g) Bongat, A. F. G.; Demchenko, A. V. *Carbohydr. Res.* **2007**, *342*, 374–406.

(2) (a) Lemieux, R. U. *Chem. Soc. Rev.* **1989**, *18*, 347–374. (b) Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495–4537. (c) Davis, B. G. *Chem. Rev.* **2002**, *102*, 579–601. (d) Lehle, L.; Strahl, S.; Tanner, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6802–6818.

(3) (a) Paulsen, H.; Kalar, C.; Stenzel, W. *Chem. Ber.* **1978**, *111*, 2358–2369. (b) Lemieux, R. U.; Ratclife, R. M. *Can. J. Chem.* **1979**, *57*, 1244–1251. (c) Paulsen, H.; Lorentzen, J. P.; Kutschker, W. *Carbohydr. Res.* **1985**, *136*, 153–176. (d) Seeberger, P. H.; Roehrig, S.; Schell, P.; Wang, Y.; Christ, W. J. *Carbohydr. Res.* **2000**, *328*, 61–69.

(4) Marcaurelle, L. A.; Bertozzi, C. R. *Glycobiology* **2002**, *12*, 69R–77R.

(5) (a) Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 9461–9462. (b) Manabe, S.; Ishii, K.; Ito, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10666–10667.

10.1021/ja106682m

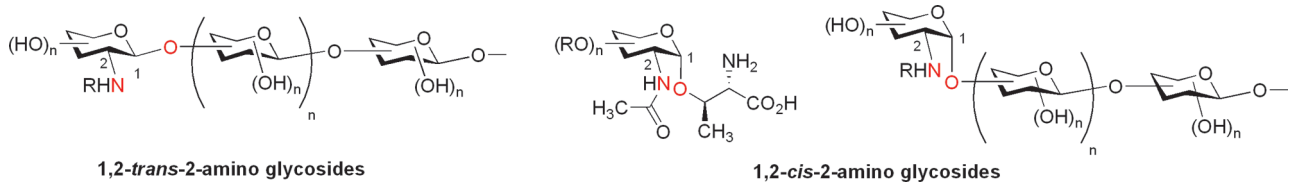
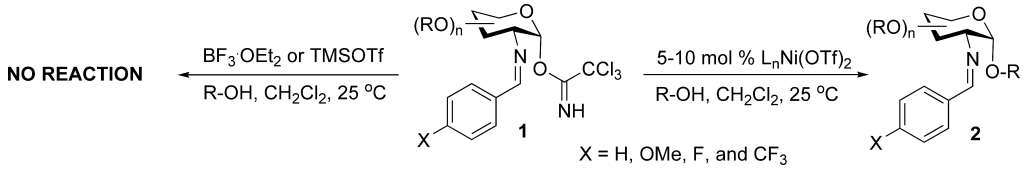
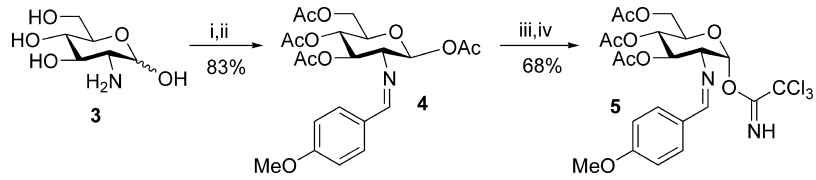


Figure 1. Representative structures of C(2)-aminosugars.

Scheme 1



Scheme 2[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.

activating reagent (PhSOTf), and undesired N-glycosylation[6] and N-sulfenylation[5] are also observed in the reaction. Additionally, the stereochemical outcome of the newly formed glycosidic bond is dependent on reactivity of alcohol acceptors.[7] Later, Schmidt reported the conjugate addition of serine/threonine to C(2)-nitro-galactals in the presence of *t*-BuOK to afford 1,2-*cis*-2-amino glycopeptides in good yields.[8] Gin has recently reported the opening of aziridines with C(1)-hemiacetal nucleophiles to form the corresponding α-*O*-glycosyl serine conjugates in good selectivity.[9] These two latter methods are limited in substrate scope.

Alternatively, use of a *p*-methoxy-benzylidene moiety as the protecting group for the C(2)-nitrogen on a glycosyl bromide to form 1,2-*cis*-2-amino glycosides was investigated over 40 years ago.[10] Its use was, however, complicated by 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, using stoichiometric amounts of HgCN provided the desired glucosides either selectively as the α-isomers[11a] or as the β-isomers[12] depending on the nature of the alcohol acceptors. In contrast, the use of AgOTf (2 equiv) as a promoter provided exclusively β-glycosides.[12] Use of *n*-pentenyl donor provided 1,2-*cis*-2-amino glycosides in moderate yields.[11b] On the other hand, no reaction was observed with use of C(2)-*p*-methoxy-benzylidene D-glucosamine trichloroacetimidate **1** as the donor under traditional Lewis acid conditions (Scheme 1).[12]

Given our own interests in merging transition-metal-catalyzed reaction methodologies with carbohydrate synthesis to stereoselectively construct a variety of α- or β-glycosidic bonds,[13] we explored the possibility for the synthesis of 1,2-*cis*-2-amino glycosides **2** (Scheme 1). The plan was to exploit the ability of cationic nickel to direct α-selective glycosylation with C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidate donors **1** (Scheme 1).[14] As a result of mild reaction conditions (5−10 mol % of nickel, 25 °C, 3−12 h) with the α-selectivity controlled by the nature of the cationic nickel−ligand complex, this new and different departure from the current state-of-the-art methods would overcome the problems associated with the preparation of the challenging 1,2-*cis*-2-amino glycosides.

Results and Discussion

Initial Studies. We initially explored C(2)-*p*-methoxy-benzylidene D-glucosamine **5** as the model donor to probe issues of both reactivity and selectivity of the coupling process under transition-metal-catalyzed reaction conditions because this glucosamine donor had been previously studied under Lewis acid conditions.[12] Thus, our goal was to develop a simple and efficient procedure for the synthesis of **5** (Scheme 2). The preparation of **5** began with commercially available D-glucosamine (**3**). Exposure of **3** to *p*-anisaldehyde and NaOH (1 M) followed by acetylation provided **4** in 83% yield over two steps.[15] Selective C(1)-*O*-deacetylation and subsequent treatment of the resulting hemiacetals with Cl_3C-CN and DBU afforded

(6) Kerns, R. J.; Zha, C.; Benakli, K.; Liang, Y.-Z. *Tetrahedron Lett.* **2003**, *44*, 8069–8072.
(7) Wei, P.; Kerns, R. J. *J. Org. Chem.* **2005**, *70*, 4195–4198.
(8) Winterfeld, G. A.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2654–2657.
(9) Ryan, D. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2008**, *130*, 15228–15229.
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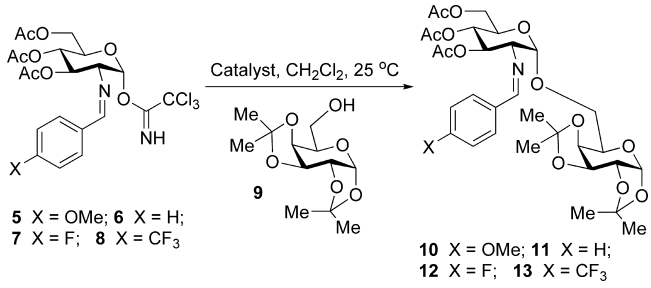
(12) Marra, A.; Sinay, P. *Carbohydr. Res.* **1990**, *200*, 319–337.
(13) (a) Schuff, B. P.; Mercer, G. J.; Nguyen, H. M. *Org. Lett.* **2007**, *9*, 3173–3176. (b) Yang, J.; Mercer, G. J.; Nguyen, H. M. *Org. Lett.* **2007**, *9*, 4231–4234. (c) Mercer, G. J.; Yang, J.; McKay, M. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2008**, *130*, 11210–11218. (d) Yang, J.; Cooper-Vanosdell, C.; Mensah, E. A.; Nguyen, H. M. *J. Org. Chem.* **2008**, *73*, 794–780. (e) Menash, E. A.; Azzarelli, J. M.; Nguyen, H. M. *J. Org. Chem.* **2009**, *74*, 1650–1657. (f) McKay, M. J.; Naab, B. D.; Mercer, G. J.; Nguyen, H. M. *J. Org. Chem.* **2009**, *74*, 4705–4711.
(14) Mensah, E. A.; Nguyen, H. M. *J. Am. Chem. Soc.* **2009**, *131*, 8778–8780.

Table 1. Optimization of Reaction Conditions for Selective Formation of 1,2-*cis*-2-Amino Glycosides[a]



entry	donor	catalyst	loading (mol %)	time (h)	yield[b] (%)	α:β[c]
1	**5**	$Pd(PhCN)_2(OTf)_2$	5	10	60	4:1
2	**5**	$Ni(PhCN)_4(OTf)_2$	5	4	95	8:1
3	**5**	$Ni(4\text{-}CF_3\text{-}PhCN)_4(OTf)_2$	5	3	90	10:1
4	**5**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	3	93	10:1
5	**5**	$Ni(4\text{-}MeOPhCN)_4(OTf)_2$	5	6	76	10:1
6	**5**	$Ni(dppe)(OTf)_2$	5	7	95	8:1
7	**5**	$Ni(4\text{-}F\text{-}PhCN)_4Cl_2$	5	10	NR	
8	**5**	AgOTf	10	10	<1%	
9	**5**	TfOH	10	5	10	3:1
10	**6**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	3	92	10:1
11	**7**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	1	96	9:1
12	**8**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	1	87	9:1

[a] The reactions were performed with 5 mol % $L_nNi(OTf)_2$, which was generated in situ from 5 mol % L_nNiCl_2 and 10 mol % AgOTf. [b] Isolated yield. [c] ^1H NMR ratio.

the corresponding trichloroacetimidate **5**. With glycosyl donor **5** in hand, attention was focused on identifying conditions for the stereoselective glycosylation reactions.

Preliminary studies examined the feasibility of the glycosylation of galactose acceptor **9** with trichloroacetimidate donor **5** in the presence of 5 mol % of cationic palladium, $Pd(PhCN)_2(OTf)_2$, as the activating reagent (Table 1, entry 1).[13e] Although the coupling process was quite sluggish, the desired disaccharide **10** was still isolated in 60% yield as a 4:1 mixture of α- and β-isomers (entry 1). Despite the fact that the reaction time, yield, and α-selectivity were not encouraging, we envisioned that additional improvement would be accomplished through the modification of the catalyst. Indeed, treatment of the coupling partners **5** and **9** with 5 mol % of cationic nickel, $Ni(PhCN)_4(OTf)_2$, generated *in situ* from $Ni(PhCN)_4Cl_2$ and AgOTf in CH_2Cl_2, afforded disaccharide **10** with an improved yield of 95% (entry 2) and a significantly higher α-selectivity (α:β = 4:1 → 8:1).[16] Additional studies focused on the effect of the nickel−ligand complex on the yields and anomeric selectivity of the coupling products (entries 3−6).[17] Gratifyingly, it was found that the more electron-withdrawing substituted benzonitrile ligands shortened the reaction time and increased the α-selectivity (entries 3 and 4). For instance, use of 5 mol % $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$ as the catalyst provided the desired disaccharide **10** in 93% yield with α:β = 10:1 (entry 4). Comparatively, the more electron-rich 4-methoxy-benzonitrile ligand increased the reaction time (entry 5). A similar coupling was also attempted with neutral $Ni(PhCN)_4Cl_2$ (entry 7), and the desired disaccharide **10** was not observed in the reaction. Because a stoichiometric amount of AgOTf had been used to activate trichloroacetimidate donors,[18] a control experiment was performed to determine if trichloroacetimidate **5** was indeed activated by 10 mol % of AgOTf. Less than 1% conversion was detected from this experiment (entry 8). To determine if triflic acid, which may be generated from cationic nickel, is the source of catalysis, the coupling of **9** with **5** was performed in the presence of 10 mol % of triflic acid (entry 9). The desired disaccharide **10** was isolated in 10% yield with α:β = 3:1. The results obtained from these control experiments suggest that the presence of the cationic nickel is important and it is not just simply acting as a Lewis acid.

The efficacy of this nickel-catalyzed α-glycosylation reaction was further explored with other *N*-substituted benzylidene trichloroacetimidate donors, **6**−**8**[19] (entries 10−12). Coupling of **9** with C(2)-*N*-benzylidene donor **6** provided disaccharide **11** in 92% yield with α:β = 10:1 (entry 10). On the other hand, switching to the electron-withdrawing *N*-substituted benzylidene donors **7** and **8** shortened the reaction time from 3 to 1 h (entries 11 and 12).[20] Overall, cationic nickel ion acts as the efficient catalyst to activate C(2)-*N*-substituted benzylidene D-glucosamine donors **5**−**8**, providing the desired disaccharides **10**−**13** in high yields and with excellent α-selectivity. In contrast, coupling of glycosyl acceptor **9** with C(2)-azido derivative of donors **5**−**8** yielded the desired disaccharide in a 2:1 α:β ratio.[21]

Substrate Scope. With the optimal conditions in hand, we were able to examine the coupling of a number of primary, secondary, and tertiary alcohols **14**−**21** with C(2)-*N*-substituted-benzylidene D-glucosamine trichloroacetimidate donors **5**−**8**. For example, glycosylation of **14** with **5** proceeded smoothly to provide disaccharide **22** in 77% yield with an α:β ratio of 20:1 (entry 1). In contrast, coupling of **14** with **5** did not occur in the presence of TMSOTf as a promoter, and use of $BF_3\cdot OEt_2$ resulted in only a trace amount of disaccharide **22** (entry 1).[12] Furthermore, the nickel chemistry is more α-selective than other methods. For example, coupling of **14** with a glycosyl bromide derivative of donor **5** in the presence of AgOTf (1.5 equiv) as the activating reagent provided the β-isomer of disaccharide **22** as the major product (α:β = 1:9).[13] On the other hand, coupling of **14** with C(2)-oxazolidinone thioglycoside donor afforded the product in 81% yield with moderate α-selectivity (α:β = 3:1).[22] The efficacy of the nickel method was further explored with an

(15) (a) Silva, D. J.; Wang, H.; Allanson, N. M.; Jain, R. K.; Sofia, M. J. *J. Org. Chem.* **1999**, *64*, 5926–5929. (b) Aly, M. R. E.; Schmidt, R. R. *Eur. J. Org. Chem.* **2005**, 4382–4392. (c) Perez, E. M. S.; Avalos, M.; Babiano, R.; Cintas, P.; Light, M. E.; Jimenez, J. L.; Palacios, J. C.; Sancho, A. *Carbohydr. Res.* **2010**, *345*, 23–32.

(16) To determine if the α:β ratio of the coupling disaccharide **10** was thermodynamically or kinetically derived, the β-isomer of **10** was subjected to the similar nickel conditions. The β-isomer was not converted to the corresponding α-isomer. This result supports our hypothesis that the anomeric ratios of the 1,2-*cis*-2-amino glycoside products are kinetically derived and are not reflective of a thermodynamic product distribution arising from postcoupling anomeric epimerization.

(17) Park, N. H.; Nguyen, H. M. *Org. Lett.* **2009**, *11*, 2433–2436.

(18) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Carbohydr. Chem.* **1993**, *12*, 131–136.

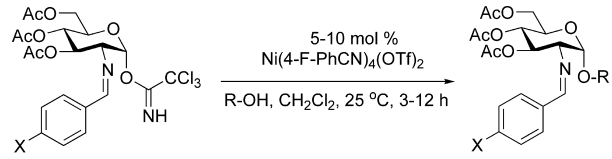
(19) Donor **6** was prepared using the same route for the preparation of donor **5**. See the Supporting Information for the preparation of donors **7** and **8**.

(20) These results suggest that electron-withdrawing benzylidene donors accelerate the rate of reaction. To further confirm this hypothesis, we performed the control experiment with a 1:1 mixture of both electron-donating 4-methoxy-benzylidene D-glucosamine donor **5** and electron-withdrawing 4-fluoro-benzylidene D-glucosamine donor **7**. In the presence of galactose **9** as the nucleophilic acceptor, a 3:1 ratio of disaccharide **12** to disaccharide **10** was observed under nickel conditions.

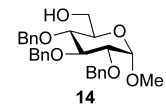
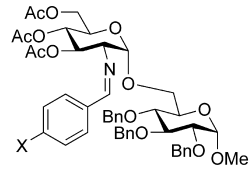
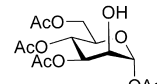
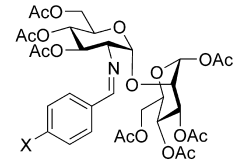
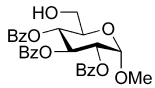
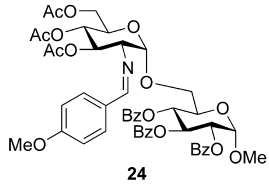
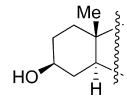
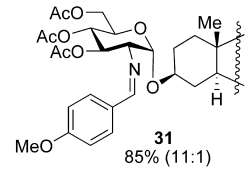
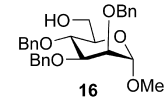
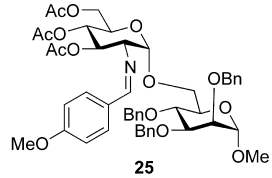
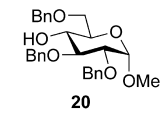
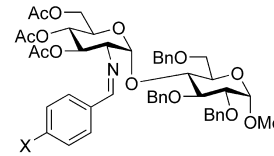
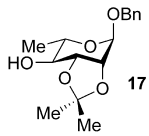
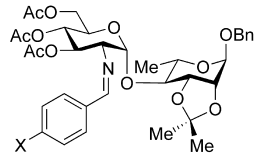
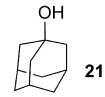
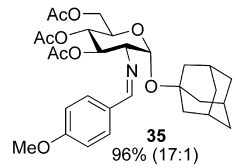
(21) Park, J.; Kawatkar, S.; Kim, J.-H.; Boons, G.-J. *Org. Lett.* **2007**, *9*, 1959–1962.

(22) Geng, Y.; Zhang, L.-H.; Ye, X.-S. *Chem. Commun.* **2008**, 597–599.

Table 2. α-Selective Coupling with C(2)-*N*-Substituted Benzylidene D-Glucosamine Donors[a]



5 X = OMe; **6** X = H; **7** X = F; **8** X = CF_3

Entry	R-OH	Products - Yield[b] (α:β)[c]	Entry	R-OH	Products - Yield[b] (α:β)[c]
1	 **14**	 X = OMe **22** 77% (20:1) X = F **23** 76% (16:1)	5	 **18**	 X = OMe **28** 97% (α only) X = H **29** 87% (α only) X = F **30** 89% (α only)
2	 **15**	 **24** 78% (15:1)	6	 **19**	 **31** 85% (11:1)
3	 **16**	 **25** 82% (10:1)	7	 **20**	 X = OMe **32** 76% (6:1) X = F **33** 80% (10:1) X = CF_3 **34** 84% (α only)
4	 **17**	 X = OMe **26** 93% (12:1) X = F **27** 88% (13:1)	8	 **21**	 **35** 96% (17:1)

[a] The reactions were performed with 5−10 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}H NMR ratio.

electron-withdrawing nucleophilic acceptor **15** (entry 2), and the desired disaccharide **24** was isolated in 78% yield with α:β = 15:1. In contrast, glycosylation of **15** with a C(2)-azido derivative of donor **5** under $BF_3 \cdot OEt_2$-mediated conditions yielded the coupling product in an 8:1 mixture of α- and β-isomers.[21] We next surveyed the possibility that secondary alcohols **17**−**19** might be the viable nucleophilic acceptors (entries 4−7). Accordingly, coupling of C(2)-hydroxyl group of mannose derivative **18** with C(2)-*N*-substituted benzylidene donors **5**−**7** provided disaccharides **28**−**30** in good yields (87−97%) and exclusively as the α-isomers (entry 5). With Kochetkov's C(2)-azido thiocyanate donor, coupling of **18** also afforded the α-isomer as the major product, albeit in lower yield (72%).[23] When dihydrocholesterol **19** was employed as a nucleophile, the corresponding glycoconjugate **31** was obtained in 85% yield with an 11:1 α:β ratio (entry 6). Under the oxazolidinone method, the glycoconjugate product was formed exclusively as the β-isomer using dihydrocholesterol as the acceptor.[24] The α-isomer, however, could be obtained when a large quantity of AgOTf (0.4 equiv) was employed to promote the anomeric epimerization of the kinetically formed β-isomer into the corresponding thermodynamically favored α-isomer.[24]

The sterically hindered alcohol acceptor **20** (Table 2) is known to provide the coupling products in poor yields and α-selectivity.[21,25] For instance, coupling of **20** with C(2)-oxazolidinone thioglycoside donor afforded the desired disaccharide in 82% yield with α:β = 2:1.[25] Under the C(2)-azido method, coupling of **20** provided the expected disaccharide exclusively as the α-isomer, albeit in lower yield (40%).[21] To demonstrate that the C(4)-hydroxyl functionality of D-glucopyranoside **20** (Table

(23) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1993**, *242*, C7–C10.

(24) Boysen, M.; Gemma, E.; Lahmann, M.; Oscarson, S. *Chem. Commun.* **2005**, 3044–3046.

(25) Geng, Y.; Zhang, L.-H.; Ye, X.-S. *Tetrahedron* **2008**, *64*, 4949–4958.

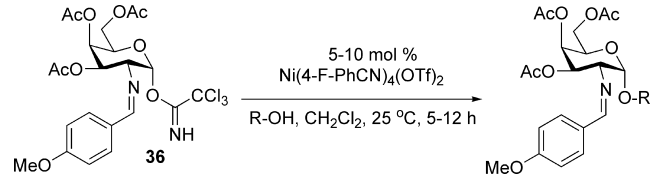
2, entry 7) can be employed as a viable nucleophile under our nickel conditions, it was coupled with glycosyl donors **5**, **7**, and **8** (Table 2, entry 7). The desired disaccharides **32**−**34** were obtained in good yields and with moderate to excellent α-selectivity. These results clearly show that the nature of the benzylidene groups on glycosyl donors plays an important role in the anomeric selectivity of the coupling products. For instance, use of an electron-donating 4-methoxy-benzylidene donor **5** provided disaccharide **32** with α:β = 6:1 (entry 7). On the other hand, coupling of glycosyl acceptor **20** with an electron-withdrawing 4-trifluoromethyl-benzylidene donor **8** afforded the corresponding disaccharide **34** exclusively as the α-isomer (entry 7). The efficiency of the nickel chemistry was further explored with tertiary alcohol **21** (entry 8). The desired glycoconjugate **35** was obtained in 96% yield and with excellent α-selectivity (α:β = 17:1). Overall, the nickel-catalyzed α-selective coupling with C(2)-*N*-substituted benzylidene D-glucosamine donors **5**−**8** provided a practical approach to get access to a variety of disaccharides and glycoconjugates in high yields and excellent levels of α-selectivity. Additionally, it does not require PhSEt as a putative nucleophile (the azide method)[21] or a large quantity of AgOTf (the oxazolidinone method)[24] in order to improve the α-selectivity. It requires only a substoichiometric amount of cationic nickel (5−10 mol %) to activate glycosyl donors **5**−**8**.

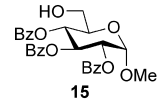
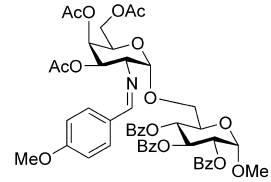
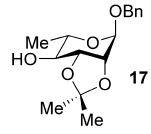
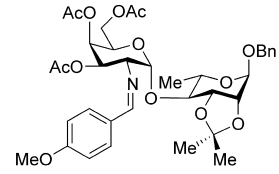
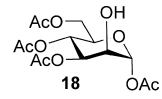
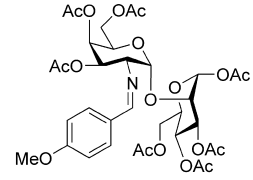
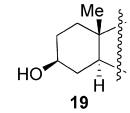
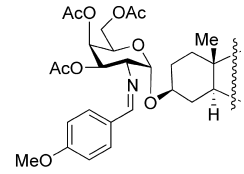
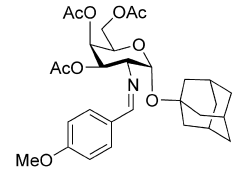
Similarly, C(2)-*N*-4-methoxy-benzylidene D-galactosamine **36**[26] was found to be a viable donor in the reaction with primary alcohol **15**, secondary alcohols **17**−**19**, and tertiary alcohol **21** (Table 3). Each coupling reaction was high yielding (74−93%) and α-selective (α:β = 10:1 to <20:1) regardless of the position of the hydroxyl moiety and the nature of the protecting groups on the nucleophilic acceptors.

To demonstrate that the current nickel method can be employed for oligosaccharide synthesis, a number of trisaccharides and tetrasaccharides were prepared from disaccharide acceptors (Table 4) and donors (Table 5). The prospect of trisaccharide synthesis was first evaluated with disaccharide nucleophiles **42**−**44** (Table 4). In the first [1 + 2] convergent approach, reaction of the disaccharide acceptor **42**[27] with C(2)-*N*-4-fluoro-benzylidene D-glucosamine donor **7** provided trisaccharide **45** (57%) with a 13:1 α:β ratio (entry 1).[28] Similarly, coupling of **42** with C(2)-*N*-4-trifluoromethyl-benzylidene electrophile **8** afforded a 56% yield of **46** with a 14:1 α:β ratio. Switching to a more electron-donating disaccharide acceptor **43**[27] provided higher yielding trisaccharides **47** and **48** (entry 2). Secondary alcohol of disaccharide acceptor **44**[29] was also a viable nucleophile, and the desired trisaccharide **49** was obtained in 76% yield with an 11:1 α:β ratio (entry 3).

In [2 + 1] and [2 + 2] convergent approaches, disaccharide trichloroacetimidates **50** and **51**[30] were investigated as feasible donors (Table 5).[28] In a [2 + 1] strategy, coupling of mannose acceptor **18** with both donors **50** and **51** provided trisaccharides **52** and **53** (entry 1) in good yields (>70%) and with excellent α-selectivity (α:β >20:1). Use of the more sterically hindered secondary alcohol **20** provided trisaccharide **53** in lower yield and α-selectivity than that of **18** (entry 2). In a [2 + 2] approach, coupling of disaccharide acceptor **43** with disaccharide donor **50** proceeded smoothly to provide tetrasaccharide **55** in 72% yield with α:β = 11: 1 (entry 3).

Table 3. α-Selective Coupling with D-Galactosamine Trichloroacetimidate[a]



Entry	R-OH	Products	Yield[b] (α:β)[c]
1			**37** 74% (14:1)
2			**38** 80% (12:1)
3			**39** 93% (α only)
4			**40** 80% (10:1)
5			**41** 84% (12:1)

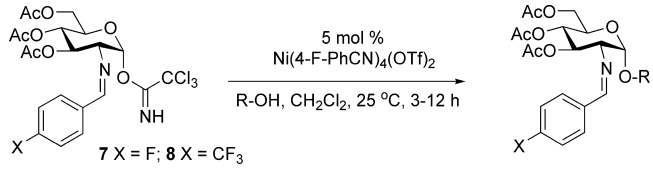
[a] The reactions were performed with 5−10 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}H NMR ratio.

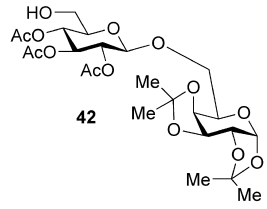
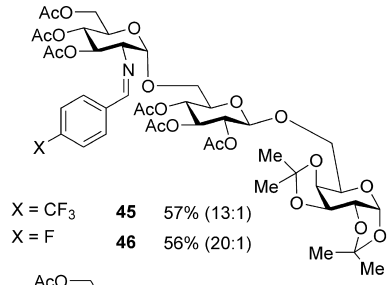
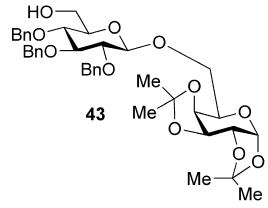
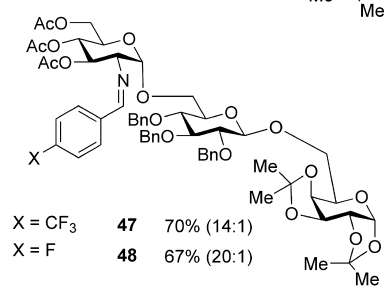
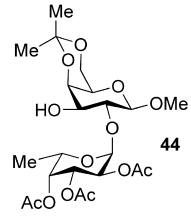
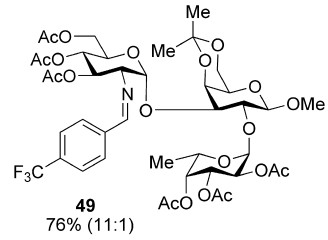
Synthetic Applications

Synthesis of Glucosamine-α-(1→4)-Linked-Glucuronic Acid Disaccharide of Heparin. During the course of our methodology studies, we became interested in the synthesis of heparin, which is a sulfated and anionic polysaccharide consisting of alternating α-(1→4)-linked-disaccharide units of L-iduronic acid or D-glucuronic acid and D-glucosamine components.[31] This polysaccharide was discovered in 1916 and introduced into clinical use in 1935.[24] It has been widely recognized to participate in a

(26) D-Galactosamine trichloroacetimidate donor **36** was prepared using the same route for the preparation of D-glucosamine donor **5**.
(27) (a) Yi, H.; Maisonneuve, S.; Xie, J. *Org.Biol.Chem.* **2009**, *7*, 3847–3854. (b) Pan, Q.; Du, Y.; Kong, F.; Pan, J.; Lu, M. *J. Carbohydr. Chem.* **2001**, *20*, 297–306.
(28) We only explored with the electron-withdrawing donors **7** and **8** because they would undergo glycosylation at a rate faster than that of 4-methoxy-benzylidene donor **5**.
(29) Meoncelli, P.; Lowary, T. L. *Aus. J. Chem.* **2009**, *62*, 558–574.
(30) The procedures for preparation of disaccharide trichloroacetimidate donors **50** and **51** are described in the Supporting Information.

Table 4. α-Selective Glycosylation of Disaccharide Acceptors[a]



Entry	Disaccharide Acceptors	Products - Yield[b] (α:β)[c]
1	 **42**	 X = CF_3 **45** 57% (13:1); X = F **46** 56% (20:1)
2	 **43**	 X = CF_3 **47** 70% (14:1); X = F **48** 67% (20:1)
3	 **44**	 **49** 76% (11:1)

[a] The reactions were performed with 5−10 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}NMR ratio.

variety of biological functions including blood anticoagulation, cell differentiation, cell growth, inflammation, and pathogen infection.[32] Currently, more than 100 heparin binding proteins have been discovered.[33] However, for most heparin binding proteins there is a lack of detailed knowledge of the ligand requirements for binding and mediating biological activity.[34] This is due to the microhetereogeneity of heparins and the difficulties associated with preparation of well-defined heparin oligosaccahrides.[35] Thus, to understand the effect of heparin structure on its biological activity, well-defined heparin sequences are required. One of the powerful tools for obtaining well-defined low molecular weight heparins (LMWH) is through chemical synthesis.[36] Although there have been remarkable advances in the synthesis of heparin oligosaccharides, limitations include long synthetic steps, low yields, and anomeric mixtures.[37] One of the major challenges in the preparation of well-defined heparin oligosaccharides is to achieve high selectivity in the synthesis of α-(1→4)-linked-disaccharide unit of D-glucuronic acid and D-glucosamine components.

Thus, our goal was to determine how D-glucuronic acid acceptors **56**−**58**[36] would behave in the nickel-catalyzed α-selective glycosylation with C(2)-*N*-substituted benzylidene D-glucosamine donors **5**−**8** (Table 6). The key model investigations in establishing the feasibility of this method involved a series of couplings of glucuronic acid acceptors **56**−**58** with

(31) (a) Karst, N. A.; Linhardt, R. J. *Curr. Med. Chem.* **2003**, *10*, 1993–2031. (b) Avci, F. Y.; Karst, N. A.; Linhardt, R. J. *Curr. Pharm. Des.* **2003**, *9*, 2323–2335. (c) Petitou, M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3118–3133. (d) Liu, H.; Zhang, Z.; Linhardt, R. J. *Nat. Prod. Rep.* **2009**, *26*, 313–321.

(32) (a) Lindahl, U.; Kusche-Gullberg, M.; Kjellen, L. *J. Biol. Chem.* **1998**, *273*, 24979–24982. (b) Bernfiled, M.; Gotte, M.; Park, P. W.; Reizes, O.; Fitzgerald, M. L.; Lincecum, J.; Zako, M. *Annu. Rev. Chem.* **1999**, *68*, 729–777. (c) Capila, I.; Lindhardt, R. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 390–412.

(33) Ori, A.; Wilkinson, M. C.; Ferning, D. G. *Front. Biosci.* **2008**, *13*, 4309–4338.

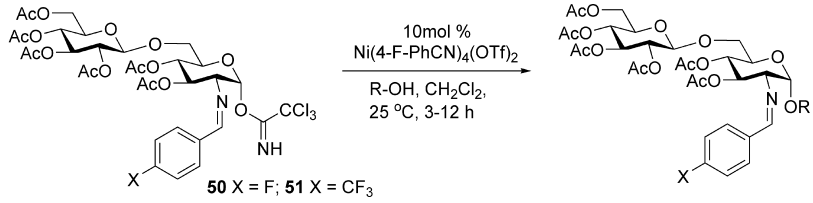
(34) Kreuger, J.; Spillman, D.; Li, J. P.; Lindahl, U. *J. Cell. Biol.* **2006**, *174*, 323–327.

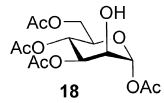
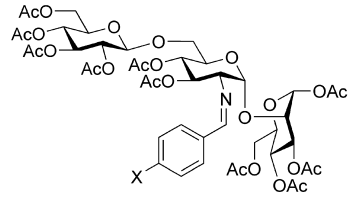
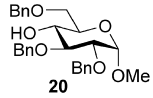
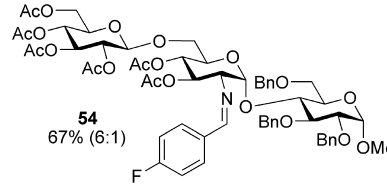
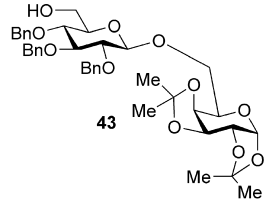
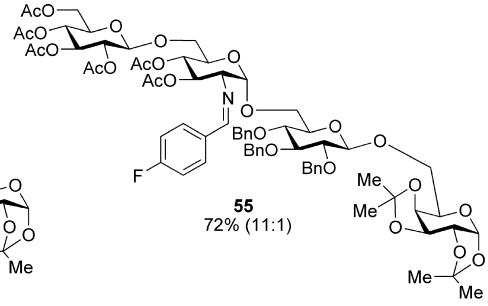
(35) Rabenstein, D. *Nat. Prod. Rep.* **2002**, *19*, 312–331.

(36) (a) Petitou, M.; van Boeckel, C. A. A. *Prog. Chem. Org. Nat. Prod.* **1992**, *60*, 143–210. (b) van Boeckel, C. A. A.; Petitou, M. *Angew. Chem., Int. Ed.* **1993**, *32*, 1671–1690. (c) Arungundram, S.; Al-Mafraji, K.; Asong, J.; Leach, F. E., III; Amster, I. J.; Venot, A.; Turnbull, J. E.; Boons, G.-J. *J. Am. Chem. Soc.* **2009**, *131*, 17394–17405.

(37) (a) Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Litjens, R. E. J. N.; Palmacci, E. R.; Seeberger, P. H. *Chem.—Eur. J.* **2003**, *9*, 140–169. (b) Codee, J. D. C.; Stubba, B.; Schiattarella, M.; Overkleef, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 3767–3773. (c) Haller, M.; Boons, G.-J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 814–822.

Table 5. α-Selective Glycosylation with Disaccharide Donors[a]



Entry	Nucleophilic Acceptors	Products - Yield[b] (α:β)[c]
1	 **18**	 X = CF_3 **52** 57% (20:1) X = F **53** 70% (24:1)
2	 **20**	 **54** 67% (6:1)
3	 **43**	 **55** 72% (11:1)

[a] The reactions were performed with 5−10 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}NMR ratio.

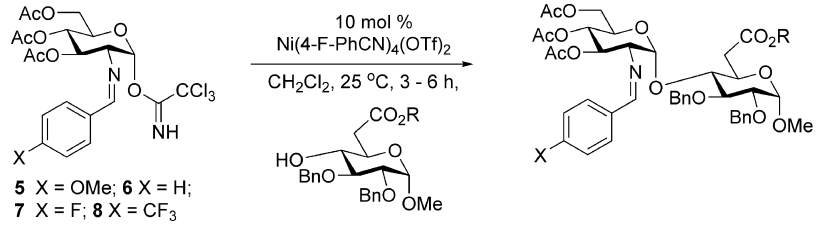
C(2)-*p*-methoxy-benzylidene glucosamine donor **5** (Table 6, entries 1−3). Use of both glucuronic acid benzyl ester **56** and allyl ester **57** (entries 1 and 2) provided disaccharides **59** and **60**, respectively, in moderate to good yields (55−84%) and with good α-selectivity (α:β = 9:1−14:1). Gratifyingly, it was found that use of glucuronic acid methyl ester **58** provided the desired disaccharide **61** exclusively as the α-isomer (entry 3). This result prompted us to further investigate the glycosylation of methyl ester D-glucuronic acid acceptor **58** with other C(2)-*N*-substituted benzylidene donors **6**−**8** (entry 4). The C(2)-*N*-*p*-trifluoromethyl-benzylidene derivative **8** was found to be the most effective donor, and disaccharide **64** was isolated in 87% yield and exclusively as the α-isomer. Compared to other systeyms,[37] our nickel method is much more α-selective. For instance, Seeberger and co-workers have reported in a modular synthesis of heparin oligosaccharides that coupling of D-glucuronic acid acceptor with a C(2)-azido trichloroacetimidate donor provided the disaccharide product in 57% yield with α:β = 3:1.[37a] Under dehydrative glycosylation conditions,[38] coupling of D-glucuronic acid acceptor with a C(1)-hydroxyl glucoazido donor afforded the desired disaccharide in 76% yield with an 7:1 α:β ratio.[37b] Because of its low reactivity, D-glucuronic acid derivatives are often masked as D-glucopyranosides that undergo selective oxidation of the C(6)-hydroxyl group to provide glucuronic acid after the assembly of oligosaccharides is complete. Even with this strategy, glycosylation of D-glucopyranoside acceptor with a C(2)-azido trichloroacetimidate still provided the coupling product in 78% yield with α:β = 3:1.[37c]

Synthesis of the Pseudodisaccharide Core of GPI Anchors. Glycosylphosphatidylinositol (GPI) anchors are a large family of glycolipids that serve to attach many eukaryotic proteins onto the outer leaflet of the cell membrane.[39] Proteins containing GPI anchors are functionally diverse and play significant roles in a variety of biological processes such as signal transduction, prion disease pathogenesis, immune response, and the patho-biology

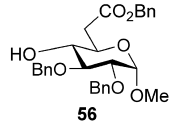
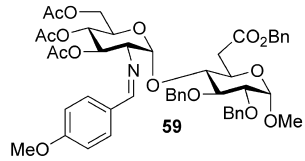
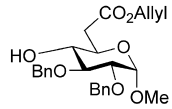
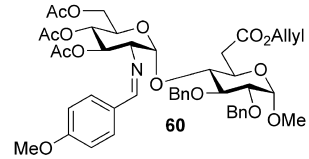
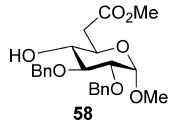
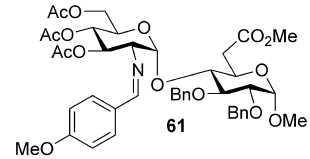
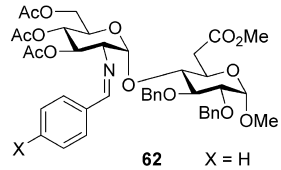
(38) (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597–7598. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279.

(39) (a) Paulick, M. G.; Bertozzi, C. R. *Biochemistry* **2008**, *47*, 6991–7000. (b) Ferguson, M. A. *J. Cell. Sci.* **1999**, *112*, 2799–2809. (c) Tiede, A.; Bastsch, I.; Schubert, J.; Orlean, P.; Schmidt, R. E. *Biol. Chem.* **1999**, *380*, 503–523.

Table 6. α-Selective Glycosylation of Glucuronic Acid Acceptors[a]



5 X = OMe; **6** X = H;
7 X = F; **8** X = CF_3

Entry	Glucuronic Acids	Products		Time	Yield[b] (α:β)[c]
1	 **56**	 **59**		5 h	55% (14:1)
2	 **57**	 **60**		6 h	84% (9:1)
3	 **58**	 **61**		6 h	71% (α only)
4	**58**		**62** X = H	5 h	68% (α only)
			63 X = F	4 h	70% (α only)
			64 X = CF_3	3 h	87% (α only)

[a] The couplings were performed with 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}NMR ratio.

of trypanosomal parasites.[40] Because of structural complexity and limited quantities, the connection between the structure of GPI anchors and their biological function in mammalian cells is difficult to study. In an effort to define the functional importance of GPI anchors, several total syntheses of GPI anchors have been reported.[41] One of the major challenges in the total synthesis of native GPI anchors is the stereoselective construction of the pseudodisaccharide unit of D-glucosamine and inositol components with high α-selectivity.[41] For instance, it has been reported that coupling of inositol with C(2)-azido glycosyl bromide in the presence of $AgClO_4$ as the activating reagent provided the desired pseudodisaccharide as a 3:1 mixture of α- and β-isomers.[42] Although switching to n-Bu_4NBr as the activating reagent provided the coupling product exclusively as the α-isomer, it took 72 h for the reaction to go to completion.[43] In the total synthesis of the *P. falciparum* GPI anchor, coupling of inositol with a C(2)-azido trichloroacetimidate provided pseudodisaccharide with an 4:1 α:β ratio.[44] In the synthesis of GPI anchor bearing unsaturated lipid chains, the desired pseudodisaccharide was formed as a 1.2:1 mixture of α- and β-isomers.[45]

To address this problem, we investigated the coupling of inositol nucleophile **65**[46] with C(2)-*N*-substituted benzylidene D-glucosamine trichloroacetimidate donors **5**−**8** (Table 7). To our delight, the coupling products **66**−**69** were formed in good yields and with excellent α-selectivity (entries 1−4). The best result was with C(2)-*N*-4-fluoro-benzylidene D-glucosamine donor **7** (entry 3), and the desired pseudodisaccharide **68** was isolated in 70% yield and exclusively as the α-anomer.

(40) (a) Nosjean, O.; Briolay, A.; Roux, B. *Biochim. Biophys. Acta* **1997**, *1331*, 153–186. (b) Chesebro, B.; Trifilo, M.; Race, R.; Meade-White, K.; Teng, C.; LaCasse, R.; Raymond, L.; Favara, C.; Baron, G.; Priola, S.; Caughey, B.; Masliah, E.; Oldstone, M. *Science* **2005**, *308*, 1435–1439.

(41) For a review, see: Guo, Z.; Bishop, L. *Eur. J. Org. Chem.* **2004**, *358*, 5–3596.

(42) Udodong, U. E.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 7886–7887.

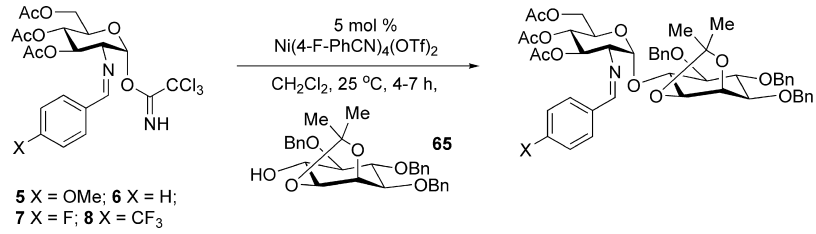
(43) Baeschlin, D. K.; Chaperon, A. R.; Green, L. G.; Hahn, M. G.; Ince, S. J.; Ley, S. V. *Chem.—Eur. J.* **2000**, *6*, 172–186.

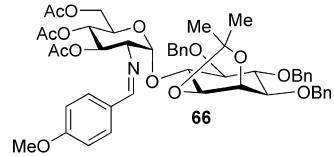
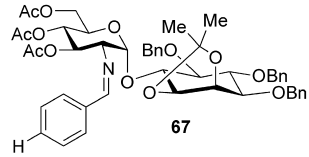
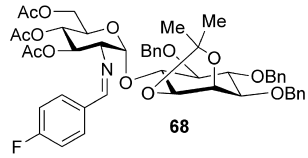
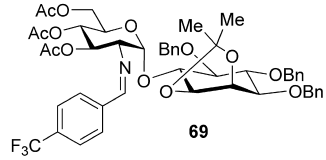
(44) Liu, X.; Kwon, Y.-U.; Seeberger, P. H. *J. Am. Chem. Soc.* **2005**, *127*, 5004–5005.

(45) Swarts, B. M.; Guo, Z. *J. Am. Chem. Soc.* **2010**, *132*, 6648–6650.

(46) Yu, F.; Guo, Z. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3852–3855.

Table 7. α-Selective Glycosylation of Inositol Acceptor[a]



Entry	Trichloroacetimidates	Pseudodisaccharides	Time	Yield (α:β)
1	**5**	 **66**	7 h	67% (α only)
2	**6**	 **67**	6 h	64% (α only)
3	**7**	 **68**	4 h	70% (α only)
4	**8**	 **69**	4 h	62% (12:1)

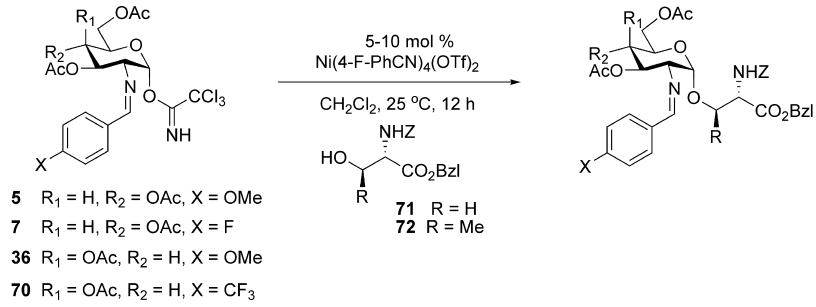
[a] The couplings were performed with 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}NMR ratio.

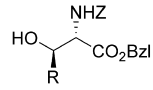
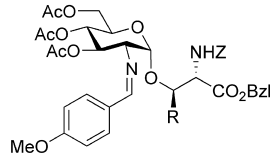
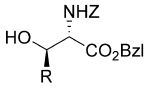
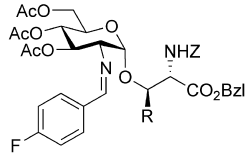
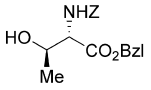
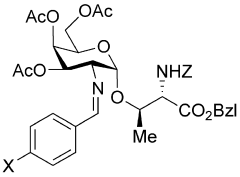
Synthesis of α-Glc- and α-GalNAc-Serine/Threonine Derivatives. Mucin-type glycoproteins carry many of the Lewis and blood group antigens and serve as ligands for the endothelial cell-surface receptors L- and P-selectin.[47] As a result, they are important mediators in normal and disease processes and have received considerable attention in cancer vaccine therapies.[48] In mucin *O*-linked glycoproteins, a GalNAc residue is α-linked to the oxygen atom on the side chain of serine (Ser) or threonine (Thr) amino acid. Thus, all mucin *O*-linked glycans contain a 1,2-*cis*-2-amino glycosidic bond. One of the major challenges in the synthesis of tumor-associated mucin antigens is to achieve high α-selectivity in the connection of a *N*-acetylgalactosamine (GalNAc) residue to the oxygen atom on the side chain of serine or threonine amino acid. Even with simple monosaccharide galactosamine donors, the stereochemical outcome of the newly formed glycosidic bond can be difficult to predict and often results in moderate α-selectivity.[49] For instance, coupling of threonine with C(2)-oxazolidinone thiogalactoside donor has been reported to provide glycopeptides as a 1:1 mixture of α- and β-isomers.[6] In the synthesis of mucin-related T_N and T_F *O*-linked antigens, it had been reported that coupling of threonine with C(2)-azido galactosamine donor afforded the desired glycopeptide as a 4:1 mixture of α- and β-isomers.[49a]

Our goal is to establish the ability of C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidates to serve as viable donors for the stereoselective synthesis of both the α-GlcNAc- and α-GalNAc-Ser/Thr derivatives (Table 8). Under our nickel conditions, coupling of serine **71** and threonine **72** with D-glucosamine trichloroacetimidate donor **5** provided the corresponding glycopeptides **73** and **74** (entry 1), respectively, in good yields (65−73%) and α-selectivity (α:β = 8:1−10:1). Use of an electron-withdrawing C(2)-*N*-4-fluorobenzylidene D-glucosamine **7** improved both the yields (75−83%) and α-selectivity (α:β = 9:1−14:1) of the resulting glycopeptides **75** and **76** (entry 2). We also explored the coupling of threonine **72** with both D-galactosamine donors **36** and **70** (entry 3). The desired glycopeptides **77** and **78** were formed, respectively, in good yields (74−81%) and with excellent α-selectivity (α:β = 14:1−15:1). Although both **36** and **70** provided the

(47) Danishefsky, S. J.; Behar, B.; Randolph, J. T.; Lloyd, K. O. *J. Am. Chem. Soc.* **1995**, *117*, 5701–5711.
(48) Danishefsky, S. J.; Allen, J. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 836–863.
(49) (a) Kuduk, S. D.; Schwarz, J. B.; Chen, X.-T.; Glunz, P. W.; Sames, D.; Ragupathi, G.; Livingston, P. O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12474–12485. (b) George, S. K.; Schwientek, T.; Holm, B.; Reis, C. A.; Clausen, H.; Kihlberg, J. *J. Am. Chem. Soc.* **2001**, *123*, 11117–11125.

Table 8. α-Selective Coupling of Serine and Threonine Amino Acids[a]



Entry	Serine/Threonine	Glycopeptides			Yield[b] (α:β)[c]
1	 **71** R = H **72** R = Me		R = H	**73**	65% (8:1)
			R = Me	**74**	73% (10:1)
2	 **71** R = H **72** R = Me		R = H	**75**	83% (9:1)
			R = Me	**76**	75% (14:1)
3	 **72**		X = OMe	**77**	74% (14:1)
			X = CF_3	**78**	81% (15:1)

[a] The couplings were performed with 5−10 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ in CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] ^{1}H NMR ratio.

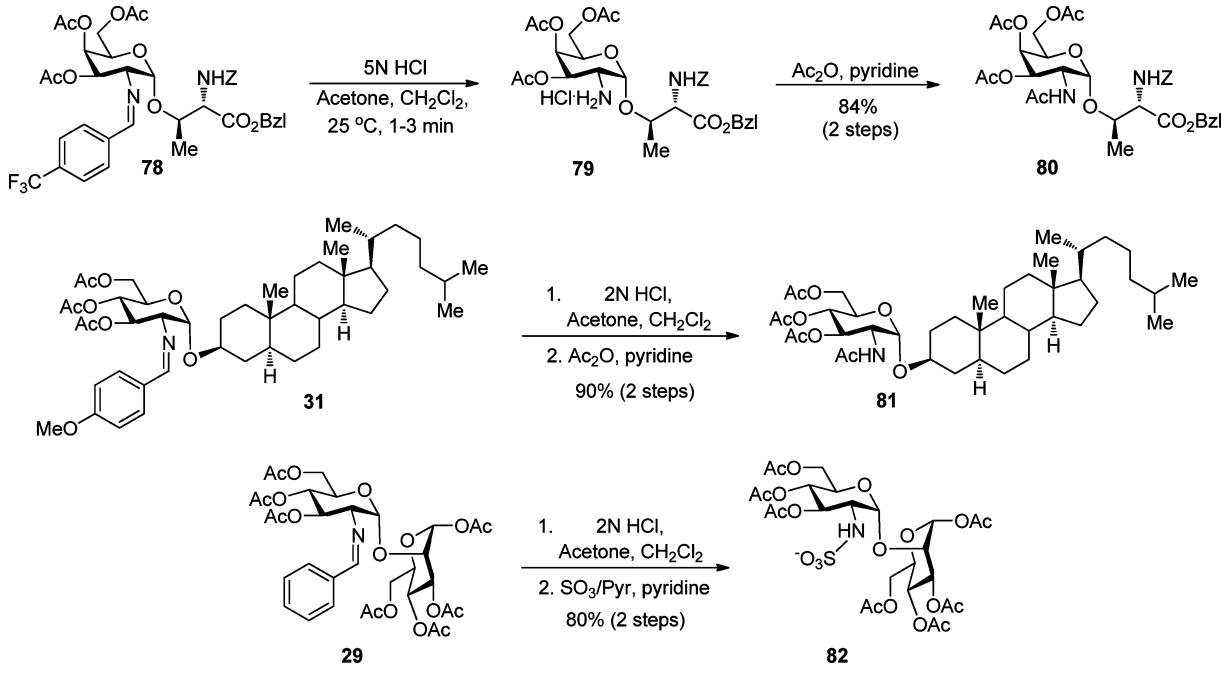
products with comparable yield and α-selectivity, the reaction was faster with an electron-withdrawing benzylidene donor **70**. Overall, our chemistry is much more α-selective than both the current state-of-the-art methods (e.g., the C(2)-azido (α:β = 4:1)[49a] and C(2)-oxazolidinone (α:β = 1:1)[6] derived donors) at accessing this family of α-glycosides.

Removal of the C(2)-N-Substituted Benzylidene Protecting Groups. Although it will be of interest to study the biological properties of these benzylidenes, it was essential to demonstrate that these benzylidenes could be converted to the corresponding *N*-acetyl or other functionalities. Because the reported conditions[15] (5 N HCl) for removal of the benzylidene protecting groups would not work well with certain acid-sensitive oligosaccharides and glycoconjugates, we screened a number of acids (TsOH, TfOH, 1 N and 2 N HCl) and found that the optimal conditions for removing the benzylidene functionality were with use of 2 N HCl (1.1 equiv), acetone/CH_2Cl_2, 25 °C, 5 min. For instance, treatment of glycopeptides **78** with 2 N HCl, acetone/CH_2Cl_2 at 25 °C for less than 3 min followed by acetylation of the resulting amine salt intermediate **79** afforded the fully protected α-GalNAc **80** in 81% yield over two steps (Scheme 3). The glycoconjugate **80** is a fully protected structure of a T_N-tumor associated mucin antigen.[49a] Similarly, removal of *N*-benzylidene functionality of **31** and **29** followed by acetylation or sulfation of the resulting amine salt intermediates provided glycoconjugates **81** and **82** in overall good yields (Scheme 3).

Mechanistic Proposal. Although the exact mechanism for the nickel-catalyzed selective α-coupling of alcohol nucleophiles with C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidates to form 1,2-*cis*-2-amino glycosides awaits further study, we suggest Figure 2 as a working hypothesis. In pathway A, nickel reversibly coordinates to both the C(1)-trichloroacetimidate nitrogen and C(2)-benzylidene group of donor **83** to form a seven-membered ring complex **84**. We reasoned that hydrogen bonding between the external oxygen nucleophile and trichloroacetamide could facilitate ionization of **84** to form the corresponding complex **85**. Ligand exchange followed by dissociation of trichloroacetamide would provide ion pair **88**. The resulting intermediate **88** then recombines in a stereoelectronically favored mode to form a five-membered ring intermediate **89**. Dissociation of the nickel species from **89** would provide 1,2-*cis*-2-amino glycoside **90**.

Alternatively, nickel can act as a mild Lewis acid (pathway B). This pathway could involve reversible coordination of $L_nNi(OTf)_2$ to the C(1)-trichloroacetimidate nitrogen of **83** to form the corresponding complex **86**. Hydrogen bonding between the external oxygen nucleophile and trichloroacetamide would promote ionization of **86**, leading to the formation of the oxocarbenium intermediate **87**. Ligand exchange between the external oxygen nucleophile and trichloroacetamide followed by coordination of $L_nNi(OR)$ to the C(2)-benzylidene nitrogen would provide the ion pair **88**, which ultimately leads to the desired 1,2-*cis*-2-amino glycoside **90**.

Scheme 3



Our first goal is to determine if the α-orientation of the trichloroacetimidate leaving group is crucial for ionization and subsequent formation of the coupling disaccharide under nickel conditions (Scheme 4). Accordingly, coupling of galactose acceptor **9** with β-trichloroacetimidate donor **5** was attempted in the presence of 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$. The coupling reaction did not proceed even after stirring for 12 h at 25 °C.

As shown in Figure 2, hydrogen bonding between the external alcohol nucleophile and the trichloroacetamide is presumed to be necessary for the facile ionization of a seven-membered ring intermediate **84** (pathway A) or a Lewis acid complex **87** (pathway B). To verify this hypothesis, the glycosylation of $TMSN_3$ or NaN_3, which lacks an acidic hydrogen, was performed with the C(2)-*N*-4-methoxyl-benzylidene D-glucosamine trichloroacetimidate **5** (Scheme 5a). In this reaction, no coupling products were observed. A second control experiment was attempted in the absence of an external alcohol nucleophile (Scheme 5b). Trichloroacetamide **91**, which was the result of the [1,3]-rearrangement of **5**, was obtained in 71% yield. The results obtained in Schemes 4 and 5 support our hypothesis that both the α-orientation of the trichloroacetimidate leaving group and hydrogen bonding are the two important factors to promote ionization of the glycosyl trichloroacetimidate donor.

Our next set of experiments were to determine if the presence of the benzylidene functionality at the C(2)-position of glycosyl trichloroacetimidate is necessary for the high α-selectivity observed in the coupling products. A first control experiment was attempted with C(2)-azido trichloroacetimidate **92** (Scheme 6a) because this donor is the most commonly used substrate under traditional Lewis acid conditions to form 1,2-*cis*-2-amino glycosides. Coupling of nucleophilic acceptor **9** with donor **92** in the presence of 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ at 25 °C afforded disaccharide **94** as a 1:1 mixture of α- and β-isomer. We also explored the use of C(2)-*N*-phenylsulfonamide trichloroacetimidate **93** (Scheme 6b) as the electrophilic donor because phenylsulfonamide had been used as the directing group for

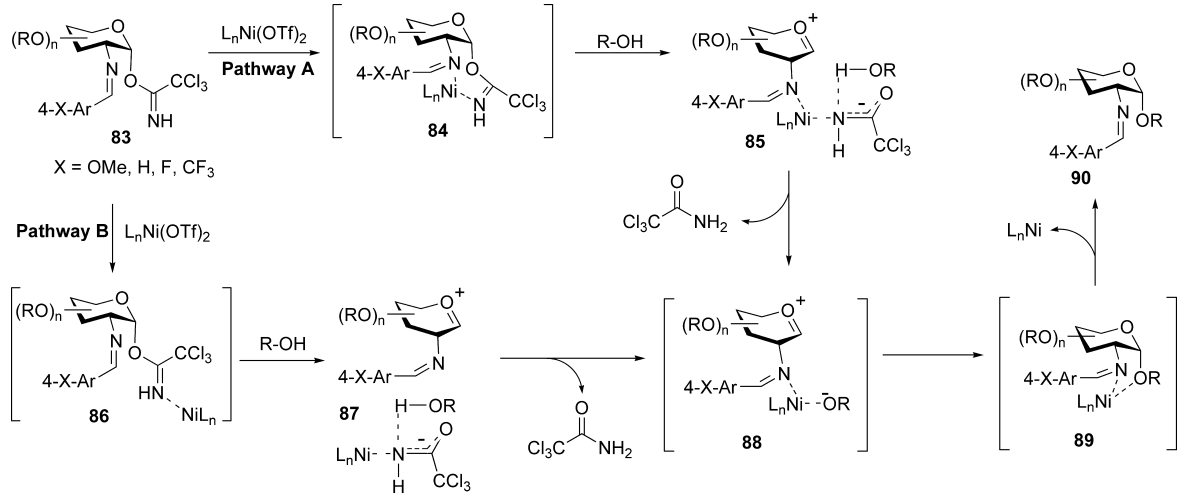
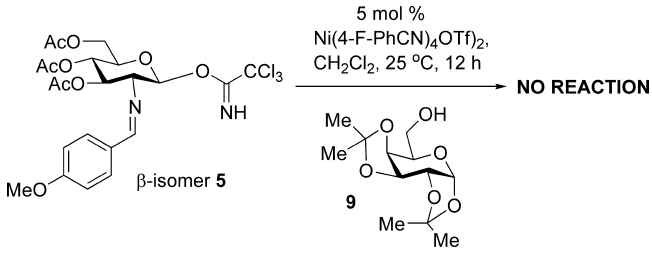


Figure 2. Proposed mechanism for nickel-catalyzed selective formation of 1,2-*cis*-2-amino glycosides.

Scheme 4



palladium-catalyzed C−H activation reactions.[50] The β-isomer **95** was isolated as the major product (α:β = 1:5) under nickel conditions (Scheme 6b). These two experiments highlight the critical role of the C(2)-*N*-substituted benzylidene functionality in the nickel-catalyzed α-selective glycosylation reaction.

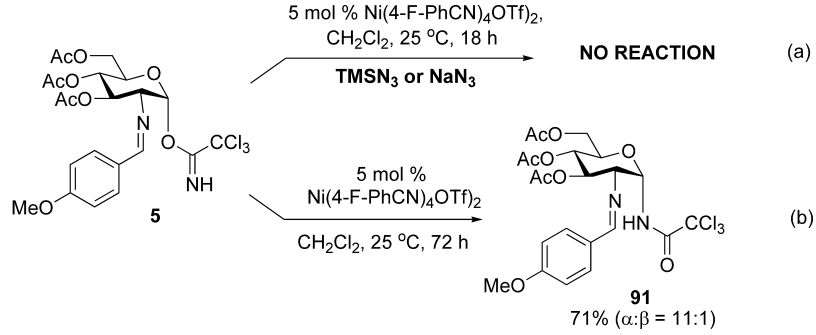
To further investigate whether coordination of nickel to both the C(1)-trichloroacetimidate nitrogen and C(2)-benzyldidene nitrogen of the glycosyl donor is essential for the coupling process to occur, coupling of galactose acceptor **9** with C(2)-*o*-methoxy-benzylidene D-glucosamine donor **96** was attempted under nickel conditions (Scheme 7). The coupling products were not observed in the reaction. This is likely due to the preferential coordination of nickel to both C(2)-benzylidene nitrogen and *o*-methoxy functionality of **96** to form a six-membered nickel complex **97**. Formation of **97** prevents nickel from coordinating to the C(1)-trichloroacetimidate nitrogen of glycosyl donor **96**. A control experiment was performed in the presence of 10 mol % of triflic acid (Scheme 7). In this coupling reaction, the desired disaccharide **97** was isolated in 15% yield with a 1:1 α:β ratio.

If the presence of the oxygen functionality at the *ortho*-position of the benzylidene group on glycosyl donor will shut down the coupling process, glycosylation of acceptor **9** with C(2)-*o*-trifluoromethyl-benzylidene D-glucosamine trichloroacetimidate donor **99** would validate this hypothesis (Scheme 8). Indeed, the coupling process proceeded smoothly with 5 mol % of Ni(4-F-PhCN)$_4$(OTf)$_2$ to provide disaccharide **100** in 81% yield and with good α-selectivity (α:β = 10:1).

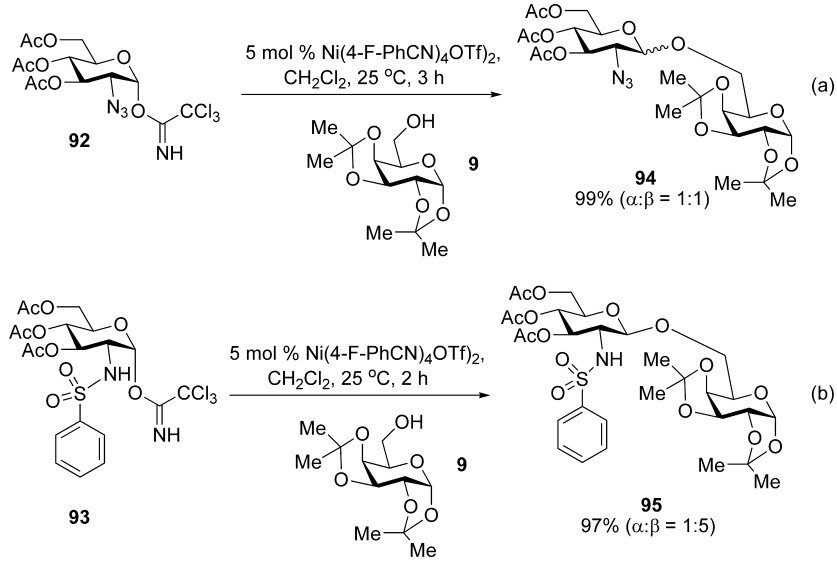
Conclusions

In summary, we have developed a novel method for the stereoselective synthesis of 1,2-*cis*-2-amino glycosides via nickel-catalyzed α-selective glycosylation with C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine trichloroacetimidate donors. These glycosyl donors are able to couple to a number of primary, secondary, and tertiary alcohol acceptors to provide glycoconjugates in good yields and with excellent α-selectivity. The current nickel method relies on the nature of the nickel−ligand complex to control the α-selectivity. The reactive sites of the nucleophiles or the nature of the protecting groups have little effect on the selectivity. Additionally, only a substoichiometric amount of nickel (5−10 mol %) is required for the coupling reaction to occur at room temperature. This method has also been applied to both disaccharide donors and acceptors to provide the corresponding oligosaccharides in high yields and with excellent levels of α-selectivity. The efficiency of the nickel chemistry has been further utilized in the preparation of the high-yielding and α-selective heparin disaccharides, GPI anchor pseudodisaccharides, and α-GluNAc/

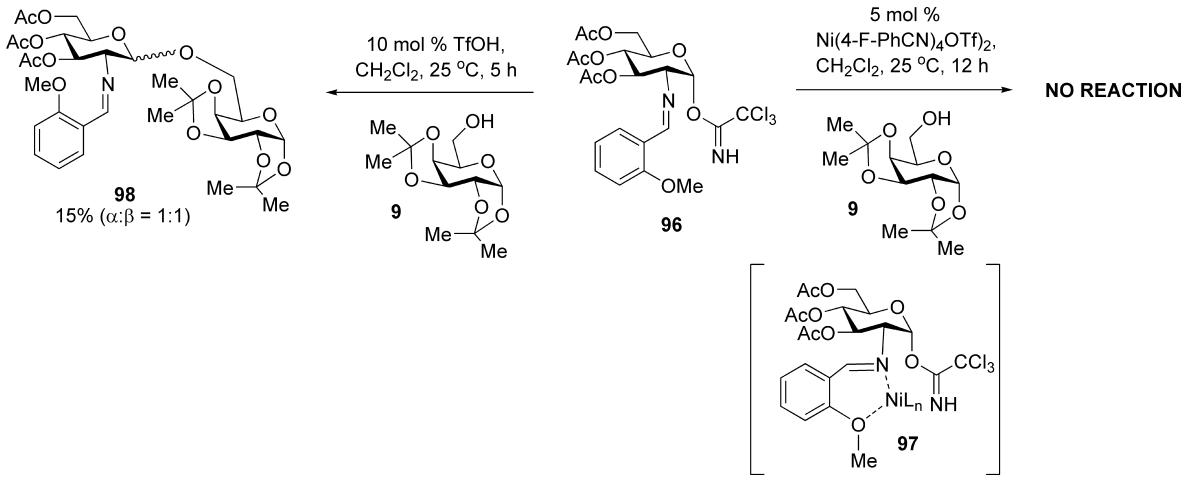
Scheme 5



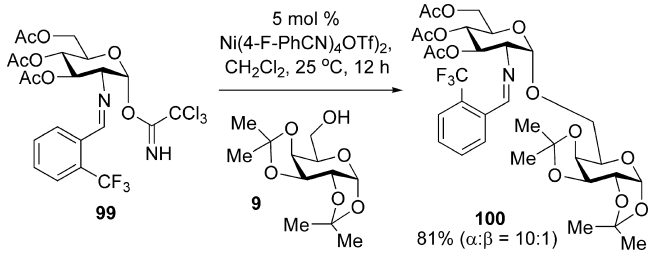
Scheme 6



Scheme 7



Scheme 8



GalNAc derivatives. Mechanistic studies suggest that the presence of the substituted benzylidene functionality at the C(2)-amino position of glycosyl donors is crucial for the high α-selectivity observed in the coupling products. Furthermore, we have demonstrated that the α-orientation of the C(1)-trichloroacetimidate group as well as the presence of the external alcohol nucleophile are necessary for the facile ionization of glycosyl trichloroacetimidate donors. We expect that insights gained from our present studies will help future advances in the stereoselective formation of 1,2-*cis*-2-amino glycosides, including developing new glycosyl donors, activating agents, and strategies for controlling α-selectivity.

Experimental Section

Representative experimental procedures are listed here. Full experimental details and spectral data for all new compounds can be found within Supporting Information.

Preparation of D-Glucosamine Trichloroacetimidate Donor 5. A 100 mL oven-dried Schlenk was charged with hemiacetal (2.4 g, 5.67 mmol, 1 equiv) and dichloromethane (30 mL). The solution was cooled to 0 °C, and trichloroacetonitrile (1.7 mL, 17.01 mmol, 3 equiv) was then added to the reaction mixture followed by DBU (0.42 mL, 2.84 mmol, 0.5 equiv). The resulting mixture was stirred at this temperature for 4 h and then concentrated in vacuo. The residue was purified by silica gel flash chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to provide trichloroacetimidate **5** (2.89 g, 90%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.56 (s, 1H), 8.22 (s, 1H), 7.61 (d, J = 10.0 Hz, 2H), 6.86 (d, J = 10.0 Hz, 2H), 6.38 (s, 1H), 5.67 (t, J = 10.0 Hz, 1H), 5.20 (t, J = 10.0 Hz, 1H), 4.34−4.32 (m, 2H), 4.13 (d, J = 10.0 Hz, 1H), 3.80 (s, 3H), 3.80−3.77 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.6, 170.0, 169.7, 163.9, 162.3, 160.8, 130.2, 128.6, 113.9, 95.8, 91.1, 71.0, 70.8, 70.4, 68.3, 61.8, 55.4, 20.7, 20.6. IR (film, cm^{-1}): ν 3334, 2961, 2839, 1752, 1674, 1642, 1605, 1579, 1512, 1246, 1065, 1021. HRMS (ESI): calcd for $C_{22}H_{25}Cl_3N_2O_9$ (M + Na) 589.0518, found 589.0525.

Preparation of Ni(4-F-PhCN)$_4$Cl$_2$.[51] A 10 mL oven-dried Schlenk flask was charged with $NiCl_2$ (129.59 mg, 1 mmol, 1 equiv) and CH_2Cl_2 (2 mL). To the resulting yellow solution was added 4-fluoro-benzonitrile (3.03 g, 25 mmol, 25 equiv). The resulting mixture was stirred at 25 °C for 24 h and then poured into hexane (40 mL). The hexane layer was decanted. The resulting yellow solid was further washed with hexane (2 × 20 mL), transferred into a preweighed vial, and dried under vacuum overnight.

Preparation of Disaccharide 10. A 10 mL oven-dried Schlenk flask was charged with D-glucosamine trichloroacetimidate donor **5** (85.2 mg, 0.15 mmol, 1 equiv), galactose acceptor **9** (50.7 mg, 0.19 mmol, 1.3 equiv), and CH_2Cl_2 (1.1 mL). The resulting solution was cooled to 0 °C, and a preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from a reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.015 mmol, 10 mol %) in dichloromethane (1 mL) for 30 min, was then added to the solution. The resulting mixture was stirred at 0 °C for 5 min and then warmed to 25 °C. The reaction mixture was stirred at the ambient temperature for 3 h, diluted with benzene (2 mL), and purified by silica gel flash chromatography (3/1, benzene/acetonitrile + 1% triethylamine) to give disaccharide **10** (93 mg, 93%, α:β = 10:1). R_f = 0.33 (benzene/acetonitrile, 3/1 + 1% TEA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.17 (s, 1H), 7.64 (d, J = 10.0 Hz, 2H), 6.86 (d, J = 10.0 Hz, 2H), 5.61 (t, J = 10.0 Hz, 1H), 5.46 (d, J = 5.0 Hz, 1H), 5.08 (t, J = 10.0 Hz, 1H), 4.89 (d, J = 5.0 Hz, 1H), 4.46 (d, J = 10.0 Hz, 1H), 4.34 (dd, J = 10.0, 4.0 Hz, 1H), 4.28−4.23 (m, 3H), 4.07 (d, J = 10.0 Hz, 1H), 4.01 (t, J = 5.0 Hz 1H), 3.80 (s, 3H), 3.80 (m, 1H), 3.72−3.70 (m, 1H), 3.54 (dd, J = 10.2, 3.2 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.83 (s, 3H), 1.52 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 170.1, 169.9, 163.6, 163.5, 162.1, 130.2, 128.6, 128,3, 114.0, 108.9, 108.7, 100.5, 96.2, 72.2, 71.5, 70.7, 70.4, 68.9, 67.8, 67.7, 66.4, 62.3, 55.4, 26.2, 25.9, 24.9, 24.0, 20.8, 20.76, 20.6. IR (film, cm^{-1}): ν 3427, 3349, 2987, 2935, 1745, 1642, 1608, 1513, 1376, 1251, 1165, 1110, 1069, 1029. J(^{13}CH) = 171 Hz (100.5 Hz). HRMS (ESI): calcd for $C_{32}H_{43}NO_{14}$ (M + H) 666.2756, found 666.2753.

Preparation of Trisaccharide 47. A 10 mL oven-dried Schlenk flask was charged with D-glucosamine trichloroacetimidate donor

(50) (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211–5215. (b) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452–6455.

(51) (a) Suzuki, H.; Ishiguro, S.-I. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 83–88. (b) Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc.* **1971**, *93*, 3360–3364. (c) Qian, H.; Pei, T.; Widenhoefer, R. A. *Organometallics* **2005**, *24*, 287–301.

7 (55.6 mg, 0.10 mmol, 1 equiv), disaccharide acceptor **43** (90.1 mg, 0.13 mmol, 1.3 equiv), and CH_2Cl_2 (0.7 mL). The resulting solution was cooled to 0 °C, and a preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from a reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (3.07 mg, 0.005 mmol, 5 mol %) and AgOTf (2.57 mg, 0.01 mmol, 10 mol %) in dichloromethane (0.5 mL) for 30 min, was then added to the solution. The resulting mixture was stirred at 0 °C for 5 min and then warmed to 25 °C. The reaction mixture was stirred at the ambient temperature for 3 h, diluted with benzene (2 mL), and purified by silica gel flash chromatography (10/1, toluene/acetonitrile + 1% triethylamine) to give the desired trisaccharide **47** (77 mg, 70%, α:β = 20:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (s, 1H), 7.78 (dd, J = 8.6, 5.5 Hz, 2H), 7.41−7.27 (m, 15H), 6.85 (t, J = 8.6 Hz, 2H), 5.74 (t, J = 9.8 Hz, 1H), 5.55 (d, J = 5.0 Hz, 1H), 5.28 (d, J = 3.5 Hz, 1H), 5.13 (t, J = 9.8 Hz, 1H), 4.99 (d, J = 11.6 Hz, 1H), 4.88 (d, J = 11.2 Hz, 1H), 4.83 (d, J = 10.6 Hz, 1H), 4.76 (d, J = 10.7 Hz, 1H), 4.70 (d, J = 10.9 Hz, 1H), 4.60 (dd, J = 7.9, 2.3 Hz, 1H), 4.38−4.31 (m, 3H), 4.26−4.19 (m, 3H), 4.13 (dd, J = 12.2, 2.0 Hz, 1H), 4.03 (t, J = 9.5 Hz, 1H), 3.98−3.94 (m, 4H), 3.65−3.59 (m, 2H), 3.54 (t, J = 9.2 Hz, 1H), 3.39−3.36 (m, 1H), 2.81 (t, J = 8.1 Hz, 1H), 2.13 (s, 3H), 2.06 (s, 3H), 1.89 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.0, 170.3, 170.0, 163.1, 139.1, 138.9, 138.8, 131.0, 130.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 116.2, 116.0, 109.6, 108.7, 104.0, 99.7, 96.5, 84.4, 82.1, 75.9, 75.8, 75.2, 74.7, 72.2, 71.5, 71.4, 70.9, 70.7, 69.1, 68.8, 67.9, 67.1, 65.4, 62.5, 26.3, 26.2, 25.2, 24.7, 21.1, 21.0, 20.9. IR (film, cm^{-1}): ν 2983, 2935, 1748, 1643, 1603, 1509, 1455, 1364, 1231, 1149, 1067, 1022. J(^{13}CH) = 173.3 Hz. HRMS (ESI): calcd for $C_{59}H_{69}NO_{18}F_3$ (M + H) 1136.4467, found 1136.4467.

Preparation of Tetrasaccharide 55. A 10 mL oven-dried Schlenk flask was charged with disaccharide trichloroacetimidate donor **50** (42 mg, 0.05 mmol, 1 equiv), disaccharide acceptor **43** (42 mg, 0.0.6 mmol, 1.2 equiv), and CH_2Cl_2 (0.45 mL). The resulting solution was cooled to 0 °C, and a preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from a reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (3.07 mg, 0.005 mmol, 10 mol %) and AgOTf (2.57 mg, 0.01 mmol, 20 mol %) in dichloromethane (0.1 mL) for 30 min, was then added to the solution. The resulting mixture was stirred at 0 °C for 5 min and then warmed to 25 °C. The reaction mixture was stirred at the ambient temperature for 7 h, diluted with benzene (2 mL), and purified by silica gel flash chromatography (9/1, toluene/acetonitrile + 1% triethylamine) to give the desired tetrasaccharide **55** (42 mg, 72%, α:β = 11:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.39−7.10 (m, 15H), 6.82 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 5.70 (t, J = 10.0 Hz, 1H), 5.53 (d, J = 5.2 Hz, 1H), 5.27−5.20 (m, 2H), 5.11−4.95 (m, 5H), 4.87 (d, J = 10.8 Hz, 1H), 4.79 (d, J = 10.8 Hz, 1H), 4.73 (d, J = 10.8 Hz, 1H), 4.66 (d, J = 10.8 Hz, 1H), 4.57−4.52 (m, 2H), 4.31−4.24 (m, 3H), 4.20−4.10 (m, 4H), 4.08−4.02 (m, 2H), 3.97−3.89 (m, 4H), 3.72−3.67 (m, 1H), 3.60−3.50 (m, 3H), 3.33 (d, J = 9.6 Hz, 1H), 2.75 (t, J = 8.8 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.85 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.3, 169.9, 169.8, 169.6, 169.4, 162.8, 138.9, 138.63, 138.62, 130.7 (d, J_{CF} = 8.2 Hz), 128.4, 128.3, 128.24, 128.20, 128.17, 128.03, 128.00, 127.7, 127.62, 127.58, 127.5, 127.4, 115.8 (d, J_{CF} = 21.5 Hz), 109.3, 108.5, 103.7, 100.9, 99.4, 96.3, 84.2, 81.9, 75.7, 75.5, 74.9, 74.4, 72.7, 71.8, 71.7, 71.4, 71.1, 70.9, 70.6, 70.4, 69.0, 68.5, 68.3, 67.8, 66.8, 64.9, 61.8, 26.03, 25.96, 24.9, 24.4, 20.79, 20.76, 20.69, 20.67, 20.6. IR (film, cm^{-1}): ν 2932, 1752, 1644, 1600, 1508, 1455, 1368, 1215, 1067, 1035. J(^{13}CH) = 179 Hz (103.7 Hz), 159 (100.9 Hz), 176 (99.4 Hz), 165 (96.3 Hz). HRMS (ESI): calcd for $C_{70}H_{85}NO_{26}F$ (M + H) 1374.5363, found 1374.5344.

Preparation of Heparin Disaccharide 64. A 10 mL oven-dried Schlenk flask was charged with D-glucosamine trichloroacetimidate donor **8** (90.87 mg, 0.15 mmol, 1 equiv), D-glucuronic acid methyl ester **58** (78.5 mg, 0.195 mmol, 1.3 equiv), and CH_2Cl_2 (1 mL). The resulting solution was cooled to 0 °C, and a preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from a reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (4.61 mg, 0.0075 mmol, 5 mol %) and AgOTf (3.85 mg, 0.015 mmol, 10 mol %) in dichloromethane (1 mL) for 30 min, was then added to the solution. The resulting mixture was stirred at 0 °C for 5 min and then warmed to 25 °C. The reaction mixture was stirred at the ambient temperature for 3 h, diluted with benzene (2 mL), and purified by silica gel flash chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired disaccharide **64** (110.8 mg, 87%, α only). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (s, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.24−7.10 (m, 8H), 6.75 (d, J = 7.0 Hz, 2H), 5.64 (d, J = 3.5 Hz, 1H), 5.53 (t, J = 10.0 Hz, 1H), 5.03 (t, J = 10.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 3.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.31 (d, J = 11.5 Hz, 1H), 4.30 (d, J = 10.0 Hz, 2H), 4.11−4.08 (m, 2H), 3.98 (t, J = 9.0 Hz, 1H), 3.85 (d, J = 10.0 Hz, 1H), 3.78 (s, 3H), 3.53 (dd, J = 9.5, 3.0 Hz, 1H), 3.46 (dd, J = 10.0, 3.0 Hz, 1H), 3.41 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 170.0, 169.8, 169.5, 162.9, 138.4, 138.1, 137.4, 128.6, 128.4, 128.2, 128.1, 128.0, 126.7, 125.6, 125.5, 98.8, 98.4, 81.2, 79.4, 75.4, 74.3, 73.5, 72.5, 70.5, 69.6, 68.3, 68.1, 61.6, 55.7, 52.5, 20.8, 20.6, 20.5. IR (film, cm^{-1}): ν 2942, 1749, 1645, 1453, 1438, 1368, 1323, 1231, 1164, 1128, 1047, 1028. J(^{13}CH) = 172.7 Hz. HRMS (ESI): calcd for $C_{42}H_{46}F_3NO_{14}$ (M + H) 846.2943, found 846.2905.

Preparation of GPI Anchor Pseudodisaccharide 68. A 10 mL oven-dried Schlenk flask was charged with D-glucosamine trichloroacetimidate donor **7** (37.8 mg, 0.068 mmol, 1 equiv), inositol acceptor **65** (40 mg, 0.082 mmol, 1.2 equiv), and CH_2Cl_2 (0.7 mL). The resulting solution was cooled to 0 °C, and a preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from a reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (2.09 mg, 0.0034 mmol, 5 mol %) and AgOTf (1.75 mg, 0.0068 mmol, 10 mol %) in dichloromethane (0.3 mL) for 30 min, was then added to the solution. The resulting mixture was stirred at 0 °C for 5 min and then warmed to 25 °C. The reaction mixture was stirred at the ambient temperature for 4 h, diluted with benzene (2 mL), and purified by silica gel flash chromatography (2/1, hexane/ethyl acetate + 1% triethylamine) to give the desired pseudodisaccharide **68** (42.2 mg, 70%, α only). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H), 7.74 (dd, J = 8.6, 5.5 Hz, 2H), 7.40−7.27 (m, 15H), 7.11 (t, J = 11.2 Hz, 2H), 5.69 (t, J = 9.8 Hz, 1H), 5.49 (d, J = 3.5 Hz, 1H), 5.07 (t, J = 10.1 Hz, 1H), 4.95 (d, J = 11.1 Hz, 1H), 4.87−4.73 (m, 5H), 4.38 (ddd, J = 10.3, 5.3, 3.0 Hz, 1H), 4.18 (t, J = 5.0 Hz, 1H), 4.14−4.05 (m, 2H), 3.97−3.90 (m, 2H), 3.81 (dd, J = 12.4, 1.8 Hz, 1H), 3.72 (dd, J = 8.1, 3.6 Hz, 1H), 3.59 (dd, J = 10.2, 3.5 Hz, 1H), 3.51 (t, J = 8.6 Hz, 1H), 2.05 (s, 3H), 1.91 (s, 3H), 1.89 (s, 3H), 1.52 (s, 3H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 170.2, 170.0, 163.1, 138.6, 138.5, 138.3, 132.4, 132.3, 130.7, 130.6, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 116.0, 115.8, 110.1, 97.4, 81.2, 80.5, 79.4, 78.4, 75.2, 74.8, 73.6, 71.9, 71.6, 68.7, 67.6, 62.0, 27.9, 25.8, 21.1, 20.1, 20.9. IR (film, cm^{-1}): ν 2936, 2870, 1745, 1644, 1601, 1509, 1454, 1366, 1222, 1152, 1125, 1025. J(^{13}CH) = 175.0 Hz. HRMS (ESI): calcd for $C_{49}H_{55}NO_{13}F$ (M + H) 884.3669, found 884.3657.

Preparation of Glycopeptide 78. A 10 mL oven-dried Schlenk flask was charged with D-galactosamine trichloroacetimidate donor **70** (90.87 mg, 0.150 mmol, 1 equiv), threonine amino acid **72** (67 mg, 0.195 mmol, 1.2 equiv), and CH_2Cl_2 (1.1 mL). The resulting solution was cooled to 0 °C, and a preformed solution of Ni(4-F-PhCN)$_4$(OTf)$_2$, which was generated in situ from a reaction of Ni(4-F-PhCN)$_4$Cl$_2$ (9.21 mg, 0.015 mmol, 10 mol %) and AgOTf (7.71 mg, 0.030 mmol, 20 mol %) in dichloromethane (1 mL) for 30 min, was then added to the solution. The resulting mixture was stirred at 0 °C for 5 min and then warmed to 25 °C. The reaction mixture was stirred at the ambient temperature for 4 h, diluted with

benzene (2 mL), and purified by silica gel flash chromatography (9/1, benzene/acetonitrile + 1% triethylamine) to give the desired glycopeptide **78** (95 mg, 80%, α:β = 15:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.18 (s, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.36−7.20 (m, 12H), 7.07 (d, J = 6.5 Hz, 2H), 6.11 (d, J = 9.0 Hz, 1H), 5.45 (bs, 1H), 5.38 (dd, J = 10.5, 2.5 Hz, 1H), 5.18 (d, J = 12.0 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 4.91 (d, J = 12.5 Hz 1H), 4.81−4.76 (m, 2H), 4.46 (d, J = 6.0 Hz, 1H), 4.39−4.33 (m, 2H), 4.11−4.10 (m, 2H), 3.62 (dd, J = 11.0, 3.5 Hz, 1H), 2.13 (s, 3H), 2.03 (s, 3H), 1.81 (s, 3H), 1.35 (d, J = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.6, 170.1, 169.8, 164.3, 164.1, 156.9, 138.0, 136.1, 134.8, 128.8, 128.7, 128.5, 128.4, 128.34, 128.3, 128.1, 127.9, 125.9, 125.5, 99.6, 74.7, 68.4, 67.9, 67.2, 67.1, 66.9, 62.2, 58.6, 20.8, 20.5, 19.4. IR (film, cm^{-1}): ν 3353, 2938, 1745, 1645, 1372, 1327, 1235, 1168, 1132. J(^{13}CH) = 170.34 Hz. HRMS (ESI): calcd for $C_{39}H_{41}FN_2O_{13}$ (M + H) 787.2684, found 787.2709.

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Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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