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Scalable Synthesis of Fmoc-Protected GalNAc-Threonine Amino Acid and T_N Antigen via Nickel Catalysis

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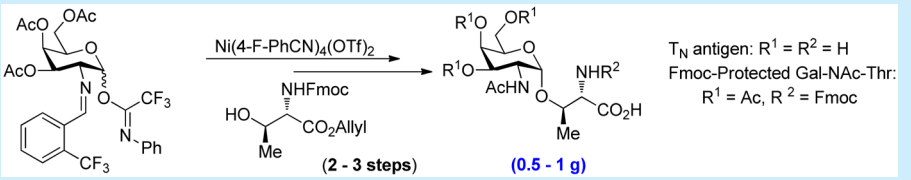
Supporting Information



ABSTRACT: The highly α-selective and scalable synthesis of the Fmoc-protected GalNAc-threonine amino acid and T_N antigen in gram scale (0.5−1 g) is described. The challenging 1,2-*cis*-2-amino glycosidic bond is addressed through a coupling of threonine residues with C(2)-*N*-*ortho*-(trifluoromethyl)benzylidenamino trihaloacetimidate donors mediated by Ni(4-F-PhCN)$_4$(OTf)$_2$. The desired 1,2-*cis*-2-amino glycoside was obtained in 66% yield (3.77 g) with α-only selectivity and subsequently transformed into the Fmoc-protected GalNAc-threonine and T_N antigen. This operationally simple procedure no longer requires utilization of the commonly used C(2)-azido donors and overcomes many of the limitations associated with the synthesis of 1,2-*cis* linkage.

Protein glycosylation can be generally divided into two major classes: *N*-linked and *O*-linked. In *N*-linked glycoproteins, an *N*-acetyl-glucosamine (GlcNAc) unit is β-linked to the amide nitrogen of an asparagine amino acid side chain.[1] In *O*-linked glycoproteins, an *N*-acetyl-galactosamine (GalNAc) unit is α-linked to the hydroxyl group of serine or threonine to generate a core structure **1** (Figure 1), commonly referred to as the T_N antigen.[2] Branching of this core structure **1** can take place at the C(3)- and/or C(6)-hydroxyl groups of GalNAc to give rise to a diverse array of structural motifs (e.g., TF antigen **2** and ST_N antigen **3**, Figure 1). These antigens are widely distributed on cell-surface mucin glycoproteins, which participate in cell adhesion events associated with cancer metastasis.[3] The T_N antigen **1**, in particular, has been found to be highly expressed by mucins on most epithelial cancers.[4] As a result, this T_N antigen has been investigated extensively as a biomarker and a therapeutic target for cancer vaccine therapy.[5]

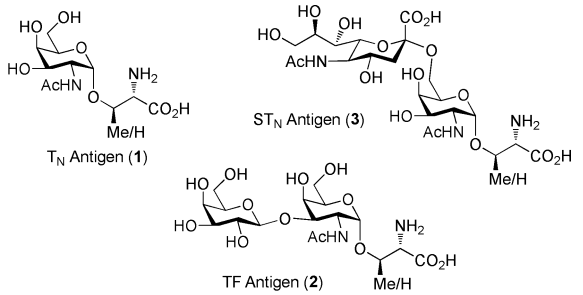
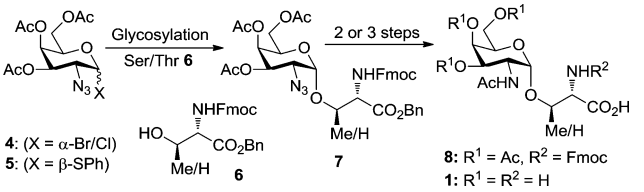


Figure 1. Structure of T_N, TF, and ST_N antigens.

In the development of cancer vaccines, well-defined and pure T_N antigen as a single tumor antigen or as a component of a polyvalent vaccine is required. However, acquiring adequate amounts of T_N antigen from natural sources in homogeneous form is challenging. In many cases, high purity T_N antigen can only be obtained by chemical and/or enzymatic synthesis.[6] In the chemical synthesis strategy, C(2)-azido donors are the most commonly used substrates for generating the T_N antigen. Early work utilized a C(2)-azido halo donor **4** (Scheme 1) in the presence of the reagent combination of Ag_2CO_3 and $AgClO_4$ as a promoter to ensure α-selectivity (α:β = 4:1) in the glycosylation reaction.[7] Another efficient synthesis of T_N antigen employed a C(2)-azido thioglycoside donor **5** (Scheme 1), and the Ph_2SO/Tf_2O system is employed to promote α-glycosylation reaction.[8] Compound **7** was further converted into Fmoc-protected GalNAc-threonine amino acid **8** (2 steps, for use in the production of full-length glycosylated proteins) and T_N antigen **1** (3 steps). A number of efficient strategies were subsequently developed for generating glycopeptides containing the T_N antigen moiety.[9,10]

Scheme 1. Previous Methods for Synthesis of T_N Antigen



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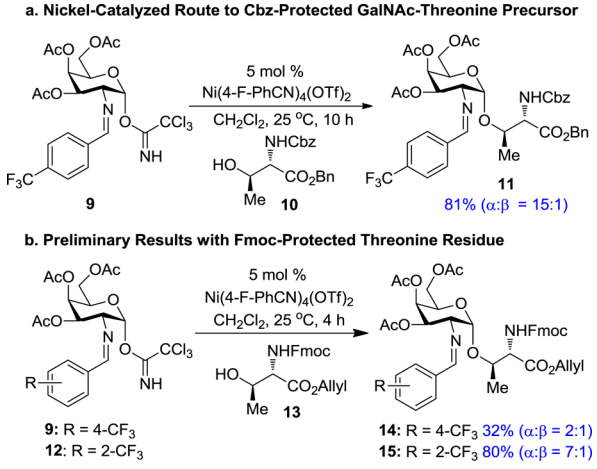
Both glycosyl amino acid **8** and T_N antigen (**1**) are readily available, but they are expensive to purchase (**8**: $303.50/25 mg and **1**: $250/mg from Sigma-Aldrich). Although high purity T_N antigen can be chemically prepared, it cannot be easily and reproducibly obtained in large quantities. Most of the existing glycosylation procedures require stoichiometric amounts of the activating agents to sufficiently activate donors, resulting in excessive waste materials.[7−9] Some of these reagents can be air- and moisture-sensitive (e.g., Ph_2SO/Tf_2O)[8] and potentially explosive (e.g., $AgClO_4$).[9] In addition, the synthesis of the commonly used C(2)-azido donors **4** and **5** (Scheme 1) is not trivial. Lemieux's azidonitration method for preparing **4** and **5** is not very diastereoselective,[11] depending on the nature of the protecting groups on glycal starting material.[12] Alternatively, diazotransfer reaction can be utilized to prepare donors **4** and **5** through direct conversion of galactosamine by the action of either trifluoromethanesulfonyl azide or imidazole-1-sulfonyl azide,[13] which are potentially explosive reagents. Although the diazotransfer method is frequently used for preparing **4** and **5**, it is unlikely to be suitable for large scale synthesis.[14] Herein, we report a scalable and reproducible protocol for the synthesis of the glycosyl amino acid **8** and T_N antigen (**1**) via nickel-mediated α-glycosylation of threonine amino acids with the C(2)-*N*-*ortho*-(trifluoromethyl)benzylidenamino trihaloacetimidate donors. This operationally simple procedure no longer requires the utilization of C(2)-azido donors and is suitable for a gram-scale synthesis of **1** and **8**.

In recent years, our group has introduced nickel-catalyzed α-stereoselective glycosylation reaction as a general platform for preparations of a variety of 1,2-*cis*-2-amino glycosides.[15] Additionally, we have illustrated that $Ni(4\text{-F-PhCN})_4(OTf)_2$ effectively promoted a coupling of Cbz-protected threonine residue **10** with C(2)-*para*-(trifluoromethyl)benzylidenamino trichloroacetimidate donor **9** to afford glycosyl amino acid **11** (Scheme 2a) in 81% yield with $\alpha:\beta$ = 15:1.[15b] We postulated that

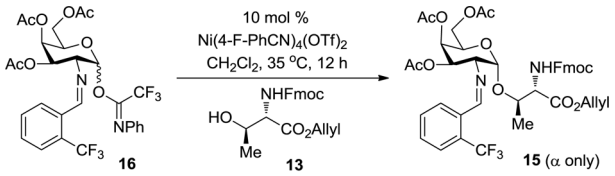
Scheme 2. Route to GalNAc-Threonine Residue via Nickel Catalysis



an analogous nickel-catalyzed α-selective coupling would be possible with Fmoc-protected amino acid **13** (Scheme 2b). Of two standard methods for the solid-phase peptide synthesis (SPPS) of glycopeptides containing the T_N antigen unit, Fmoc-based chemistry is more utilized than Boc-based chemistry.[1b] Unfortunately, employing 5 mol % of $Ni(4\text{-F-PhCN})_4(OTf)_2$ to promote the coupling of **13** with donor **9** only resulted in a 32% yield of **14** (Scheme 2b) with $\alpha:\beta$ = 2:1. Alternatively, use of C(2)-*N*-*ortho*-(trifluoromethyl)benzylidenamino donor **12** (Scheme 1b) improved both the yield (32% → 80%) and α-selectivity ($\alpha:\beta$ = 2:1 → 7:1). Although α-trichloroacetimidate donor **12** acted as an effective donor, it was a minor anomer resulting from the reaction of hemiacetal with Cl_3CCN and DBU ($\alpha:\beta$ = 1:3). Unfortunately, reaction of the β-anomer of **12** with **13** resulted in no reaction.

On the basis of our recent successful results with the use of *N*-phenyl trifluoroacetimidates as effective donors,[15d−f] we hypothesize that triacetyl galactosamine donor **16** (Scheme 3),

Scheme 3. Reproducible and Gram-Scale Synthesis of Glycosyl GalNAc-Threonine Compound 15



a.	0.808 g (1.0 equiv)	0.585 g (1.2 equiv)	74%, 0.782 g
b.	0.947 g (1.0 equiv)	0.685 g (1.2 equiv)	63%, 0.779 g
c.	5.730 g (1.28 equiv)	2.710 g (1.0 equiv)	66%, 3.77 g

bearing the C(2)-*N*-*ortho*-(trifluoromethyl)benzylidene group, is a suitable starting material for the gram-scale synthesis of glycoside **15**, its corresponding Fmoc-protected threonine amino acid **8**, and T_N antigen (**1**). In contrast to our existing systems (Scheme 2a−b),[7−10] this process can promote the glycoylsation with both α- and β-anomers of **16**[16] and only relies on substoichiometric amounts of the nickel catalyst.

While it was known that $Ni(4\text{-F-PhCN})_4(OTf)_2$ effectively promoted the glycosylation of a wide variety of carbohydrate acceptors with C(2)-*ortho*-(trifluoromethyl)benzylidenamino *N*-phenyl trifluoroacetimidate donors,[15e,f,17] it was unclear if the reaction of Fmoc-protected threonine amino acid **13** with substrate **16** would proceed with high yield and α-selectivity. Importantly, it was still unclear if the nickel method can be utilized in a large scale preparation of glycosyl amino acid **15** (Scheme 3). We were delighted to find that by employing only 10 mol % $Ni(4\text{-F-PhCN})_4(OTf)_2$ the coupling reaction reached completion in 12 h at 35 °C to afford the desired product **15** in 74% yield with exclusive α-anomeric selectivity (Scheme 3a). Purification of the glycosyl amino acid **15**, however, was tedious due to the closeness in R_f value of the threonine acceptor **13** to the desired product **15**. In the second trial, we glycosylated **13** with *N*-phenyl trifluoroacetimidate donor **14** on a similar scale (Scheme 3b) and obtained a comparable yield and selectivity (63%, α only). The yield in this second run was slightly lower because we tried two different purification methods (manual and automated chromatography) to separate **15** from unreacted threonine donor **13**. Unfortunately, it was not successful. Anticipating that this problem would be exacerbated at a larger scale, we made the threonine acceptor **13** the limiting reagent (Scheme 3c) and isolated 3.77 g of pure product **15** in 66% yield with α-only selectivity.[18] Overall, the results obtained in Scheme 3 have illustrated the high α-selectivity and scalability of the nickel-catalyzed glycosylation reaction under mild and operationally simple conditions.

Further investigation of the scope showed that a glycosylation reaction could be realized using 10 mol % of the nickel catalyst, $Ni(4\text{-F-PhCN})_4(OTf)_2$, with other donors and a number of

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Fmoc-protected threonine amino acids to afford the desired 1,2-*cis*-2-amino glycosides **17**–**21** (Figure 2) in good yields (61–86%) with excellent α-selectivity (α:β = 14:1, α only). The terminal alkyne of product **18** is capable of conjugating to biorthogonal azide, via click chemistry,[19] for incorporation into a wide variety of biomolecules.[20] This alkyne can also conjugate to a linker possessing the azide functionality to form the corresponding polymerizable monomer, which can then undergo ring-opening metathesis polymerization[21] to generate highly clustered T_N antigens for potential use as antitumor vaccine candidates.[22] On the other hand, both glycosyl amino acids **19** and **20** can be further functionalized to generate the ST_N antigen (**3**, Figure 1). The Cbz-protected threonine amino acid was also compatible with this nickel system, providing the desired glycoside product **21** (Figure 2) in 67% yield as a single α-anomer.

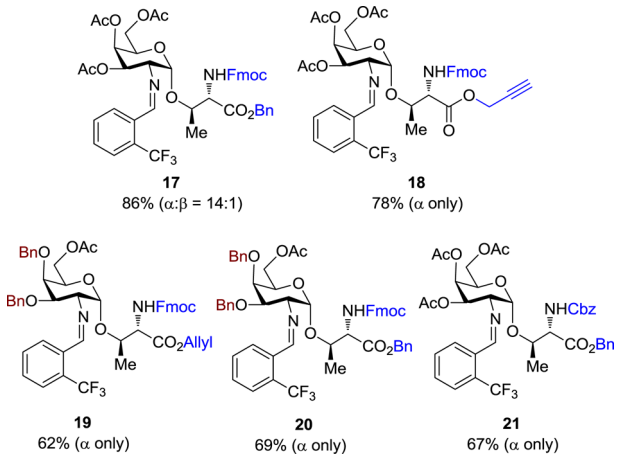
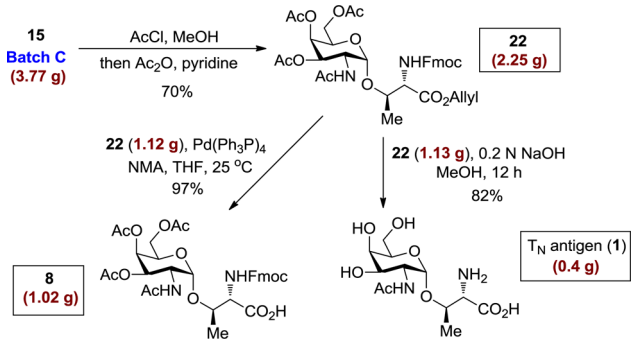


Figure 2. Scope of the reaction with threonine amino acids.

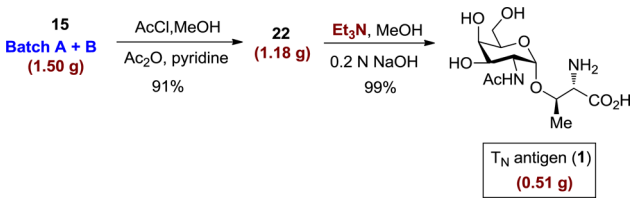
Since the Fmoc-protected GalNAc-threonine amino acid **8** (Scheme 4) is a versatile building block required for SPPS of mucin-type glycopeptides,[1b] we next investigated the mild conditions for converting glycosyl amino acid **15** into **8**. The previous conditions (2–5 N HCl, acetone, 25–50 °C)[15] for the exchange of C(2)-*N*-benzylidenamino functionality with a *N*-acetyl group to form **22** (Scheme 4) may not be suitable for use in a large scale synthesis. Using the product **15** from Scheme 3c, we found that the benzylidene group could be removed with acetyl chloride (1.6 equiv) in methanol at 25 °C. Subsequent acetylation of the amine salt intermediate provided the desired Fmoc-protected GalNAc-threonine **22** in 70% yield (Scheme 4). One-half of **22** from batch C (Scheme 4) was utilized to synthesize 1.02 g of Fmoc-protected GalNAc-threonine amino acid **8** (97% yield) using $Pd(Ph_3P)_4$ in THF and NMA at 25 °C for 1 h. Global hydrolysis of the other half of **22** from batch C with sodium hydroxide in methanol provided 0.4 g of the T_N antigen (**1**) in 82% yield. While a high yield of **1** was obtained, we found these conditions to be insufficient in fully deprotecting the Fmoc group.

Scheme 4. Gram-Scale Synthesis of T_N Antigen and Fmoc-Protected GalNAc-Threonine Amino Acid: First Conditions



We hypothesized that addition of triethylamine alongside sodium hydroxide in methanol would facilitate quantitative global deprotection of the intermediate **22** to produce the T_N antigen (**1**). To test our hypothesis, batches A and B of 1,2-*cis*-2-amino glycoside **15** from Scheme 3a and 3b were combined and transformed to 1.18 g of GalNAc-threonine amino acid intermediate **22** (Scheme 5). We are delighted to report that global deprotection of **22** in the presence of triethylamine and sodium hydroxide occurred with almost quantitative yield (99%, Scheme 5).

Scheme 5. Gram-Scale Synthesis of the T_N Antigen (1): Second Conditions



In summary, we have illustrated a highly α-selective 1,2-*cis*-2-amino glycosylation reaction utilizing a substoichiometric amount of $Ni(4\text{-F-PhCN})_4(OTf)_2$ to mediate the coupling of a number of Cbz- and Fmoc-protected threonine amino acids with C(2)-*ortho*-(trifluoromethyl)benzylideneamino *N*-phenyl trifluoroacetimidate donors. This methodology demonstrates the utility of our catalytic, selective glycosylation method for a gram scale preparation of glycosyl 1,2-*cis*-2-amino acids and their subsequent transformation into the corresponding Fmoc-protected GalNAc-threonine amino acid and T_N antigen. This operationally simple procedure no longer requires utilization of the commonly used C(2)-azido donors, which are often prepared via the potentially explosive diazotransfer reaction. As the scalable, catalytic, and stereoselective synthesis of complex oligosaccharides and glycoconjugates continues to develop, we anticipate that this nickel-catalyzed glycosylation methodology will have an impact on the strategies used for the preparation of biologically active carbohydrate molecules.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(16) We have also previously conducted a control experiment to determine if the β-isomer of *N*-phenyl trifluoroacetimidate undergoes isomerization to its corresponding α-isomer prior to the coupling event.[15f] The β-isomer did not convert to the corresponding α-isomer. As the reaction progressed, the β-isomer converted into the undesired glycal product. This result suggests that *N*-phenyl trifluoroacetimidate donors may react via a different pathway compared to trichloroacetimidate donors under nickel conditions.

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