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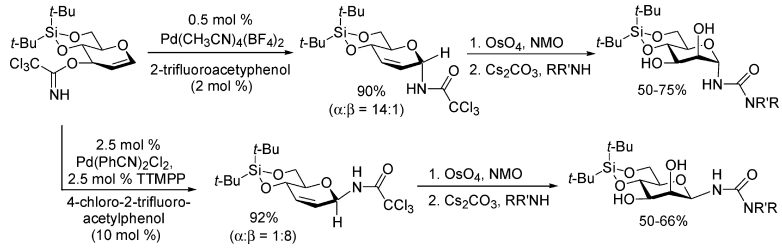

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Palladium(II)-Catalyzed Rearrangement of Glycal Trichloroacetimidates: Application to the Stereoselective Synthesis of Glycosyl Ureas

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Abstract: The research on the area of glycosyl urea derivatives, in which the O- and N-glycosidic bonds are replaced with the urea-glycosidic linkages, has recently emerged with applications in the field of aminoglycoside antibiotics. We have developed a novel method for the stereoselective synthesis of α- and β-glycosyl ureas via Pd(II)-catalyzed rearrangement of glycal trichloroacetimidates. In our approach, the α- and β-selectivity at the anomeric carbon of *N*-glycosyl trichloroacetamides depends on the nature of the palladium−ligand catalyst. While the cationic Pd(II)-**L-4** (2-trifluoroacetylphenol) complex promotes α-selectivity, the neutral Pd(II)-TTMPP-**L-5** (4-chloro-2-trifluoroacetylphenol) complex favors β-selectivity. The resulting α- and β-*N*-glycosyl trichloroacetamides were further coupled with a diverse array of primary and hindered secondary nitrogen nucleophiles to provide the corresponding glycosyl ureas in moderate to good yields and with no loss of stereochemical integrity at the anomeric carbon. We have further demonstrated the utility of *N*-glycosyl trichloroacetamides as robust and versatile intermediates in the synthesis of unsymmetrical urea-linked disaccharides and trisaccharide.

Introduction

The glycosyl ureas are found in nature as a structural unit of the glycocinnamoylspermidine antibiotics.[1] In recent years, research on the area of N-linked-glycopeptide mimics,[2] neoglycoconjugates,[3] and pseudooligosaccharides,[4] in which the *O*- and N-glycosidic bonds are replaced with the urea−glycosidic linkages, has emerged with the application in the development of antidiabetic agents[5] and aminoglycoside antibiotics.[6] The modification of the structures of naturally occurring carbohydrates has received considerable attention because oligosaccharide chains are susceptible to chemical or enzymatic hydrolysis,[7] thus causing the cleavage of O-glycosidic bonds as well as the degradation of the glycoconjugates. Therefore, it is desirable to have access to modified structures such as glycosyl ureas that are more stable under biological conditions and still maintain the properties of the natural compounds. There are only a few methods reported, however, for the stereoselective construction of glycosyl urea,[8] and in particular, the stereoselective synthesis of α-glycosyl ureas is still limited.[2a,3,9]

We report herein a novel method for the stereoselective synthesis of α- and β-glycosyl ureas via Pd(II)-catalyzed glycal imidate rearrangement.[10] In our approach, the nature of the palladium−ligand complex controls the anomeric selectivity (Scheme 1).[11] The cationic Pd(II), which promotes ionization of the glycal imidate **1** by coordinating to the imidate nitrogen,[12] results in the formation of α-*N*-glycosyl trichloroacetamide **2**. In contrast, use of neutral Pd(II) promotes a concerted-type

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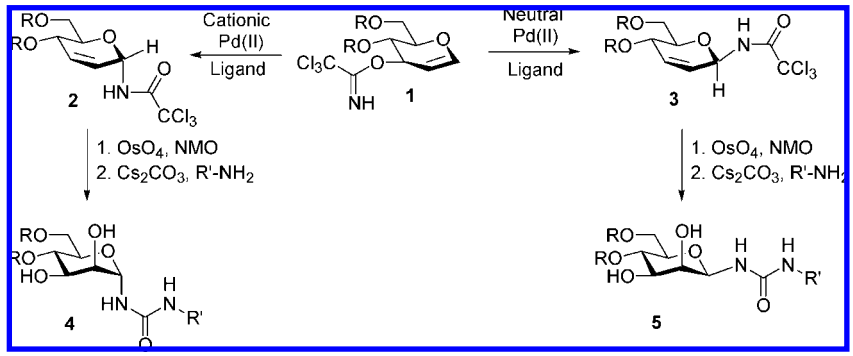
Scheme 1



mechanism to provide β-*N*-glycosyl trichloroacetamide **3**.[13] The resulting α- and β-*N*-glycosyl trichloroacetamides **2** and **3** are further transformed into the corresponding glycosyl ureas **4** and **5**, respectively, in a two-step procedure. The advantage of using the palladium catalysis is that both α- and β-*N*-glycosyl trichloroacetamides can be synthesized from the same starting material with good to excellent anomeric selectivity under mild conditions. Additionally, the starting glycal trichloroacetimidate can be readily prepared by the combination of glycal, trichloroacetonitrile, and a catalytic amount of DBU. Although the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates is pioneered by Overman,[14] this method has never been employed in carbohydrate synthesis to control the anomeric selectivity of the *N*-glycosyl trichloroacetamides.

Results and Discussion

A. Pd(II)-Catalyzed Glycal Imidate Rearrangement. A successful Pd(II)-catalyzed rearrangement of glycal trichloroacetimidates requires the development of a suitable palladium−ligand complex that can differentiate between the cyclization-induced rearrangement and ionization−recombination pathways (Figure 1). The cyclization-induced rearrangement of allylic trichloroacetimidates catalyzed by the chiral Pd(II) catalyst has been thoroughly studied by Overman and Bergman.[13] It was envisioned that a complementary method for glycal trichloroacetimidate rearrangement would arise from coordination of the neutral Pd(II)−ligand catalyst to the double bond of **1** to form π-complex **6**, which is activated toward nucleophilic attack by the imidate nitrogen to form σ-complex **7** (Figure 1). Subsequent Grob-like fragmentation followed by dissociation of the amide from palladium yields β-*N*-glycosyl trichloroacetamide **3**. Alternatively, because the cationic palladium(II) species acts as Lewis acid catalyst,[15] it would coordinate to the imidate nitrogen of **1** to form **8** which subsequently undergoes ionization to generate ion pair **9**.[12] The intermediate **9** then recombines in a stereoelectronically favored mode to form α-*N*-glycosyl trichloroacetamide **2**.

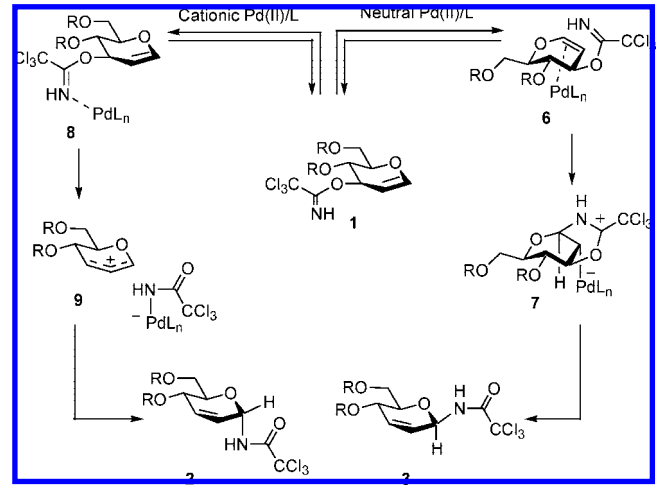


Figure 1. Proposed mechanism for palladium(II)-catalyzed rearrangement of glycal imidates.

The feasibility of the palladium-catalyzed allylic imidate rearrangement outlined in Figure 1 was examined by treatment of glucal imidate **10** with 2.5 mol % of $Pd(PhCN)_2Cl_2$ in CH_2Cl_2 at 25 °C for 2 h to provide a 1:1 mixture of α- and β-*N*-glycosyl trichloroacetamide **11** in 60% yield (Table 1, entry 1). Addition of 4 Å molecular sieves significantly increased the yield of **11** (entry 2). It was anticipated that the stereoselectivity at the anomeric carbon would depend on the ligand on palladium.[11] Accordingly, glucal imidate **10** was treated with a preformed solution of $Pd(PhCN)_2Cl_2$ and Ph_3P, and *N*-glycosyl trichloroacetamide **11** was isolated in 83% yield with $\alpha:\beta = 1:2$ (entry 3). A variety of Buchwald's bulky biaryl phosphine ligands were investigated because these ligands are resistant toward oxidation by molecular oxygen.[16] Since these ligands are electron-rich, they could potentially reduce Pd(II) to Pd(0) in the reaction; thus, only a 1:1 mixture of palladium and ligand was investigated. With the use of RuPhos, *t*-BuX-Phos, and JohnPhos as the phosphine ligands, the anomeric selectivity was improved, favoring the β-anomer (entries 5−7). Employing tris(trimethoxyphenyl)phosphine (TTMPP) as the ligand led to an improvement of both the yield and the β-selectivity (entry 8). These results clearly suggest that the bulky phosphine ligands promote the cyclization-induced rearrangement[13] over the ionization of glycal imidate **10**[12] to favor the formation of β-*N*-glycosyl trichloroacetamide **11**.

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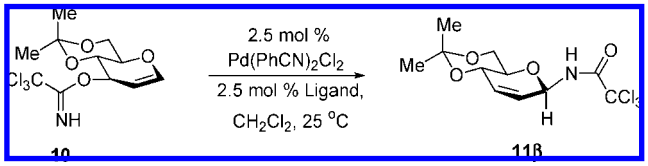
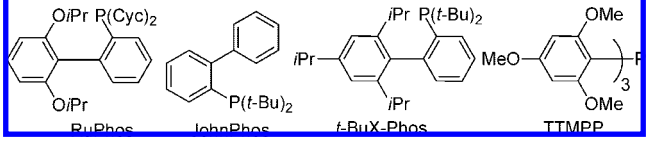
Table 1. Neutral Pd(II)-Catalyzed Stereoselective Formation of β-*N*-Glycosyl Trichloroacetamide[a]



Entry	Phosphine Ligand	Additive	Time	Yield[b]	α:β[c]
1	none	none	2 h	60%	1:1
2	none	4Å MS	2 h	75%	1:1
3	Ph_3P	none	16 h	83%	1:2
4	BINAP	none	20 h	85%	1:2
5	RuPhos	none	16 h	77%	1:3
6	*t*-BuX-Phos	none	25 h	73%	1:4
7	JohnPhos	none	23 h	75%	1:7
8	**TTMPP**	**none**	**16 h**	**89%**	**1:7**



[a] All reactions were carried out in CH_2Cl_2 (0.2 M) with 2.5 mol % $Pd(PhCN)_2Cl_2$ and 2.5 mol % phosphine ligand. [b] Isolated yield. [c] ^1H NMR ratio.

Although the bulky phosphine ligands provided the product with moderate to good β-selectivity, it took 16−25 h for the reaction to go to completion. This suggests that the rate of nucleophilic attack by the imidate nitrogen to the palladium−olefin complex such as **6** (Figure 1) may not be fast enough. Additionally, the rate difference between the cyclization-induced rearrangement pathway and the ionization pathway is not large enough. An alternative approach is to increase the electrophilicity of double bonds of glycal imidates by altering the electronic nature of the palladium−ligand complex. Furthermore, the catalyst must effectively control the relative population of the α- and β-anomers. Toward this end, several σ-donor ligands were explored (Scheme 2) in conjunction with the bulky phosphine ligands.

A standard set of conditions that employed 2.5 mol % $Pd(PhCN)_2Cl_2$, 2.5 mol % phosphine ligand, and 10 mol % σ-donor ligand were adopted (Table 2). Gratifyingly, it was found that addition of salicylaldehyde[17] (**L-1**) significantly shortened the reaction time and increased the β-selectivity (entries 1 and 2), providing the desired *N*-glycosyl trichloroacetamide **11** in good yield. We also examined whether the reaction temperature effected the selectivity; increasing or decreasing the reaction temperature only decreased the β-selectivity (entries 3 and 4). This trend with temperature suggests that while heat can lead to faster rearrangement, it can also lead to faster equilibration between the two pathways outlined in Figure 1. On the other hand, cooling can lead to slower cyclization-induced rearrangement pathway and allow equilibration between the two pathways; thus, the β-selectivity was decreased. A control experiment without TTMPP was performed to determine if the bulky phosphine ligand is necessary for the β-selectivity (entry 5). A 1:2 mixture of α- and β-isomer **11** was detected in the reaction. Thus, the combination of the bulky phosphine ligand and salicylaldehyde (**L-1**) increased the β-selectivity as well as shortened the reaction time. The more electron-rich ligands (**L-2** and **L-3**) significantly increased the reaction time and lowered the β-selectivity (entries 6 and 7). On the other hand, switching to the more electron-withdrawing ligands[18] (**L-4** and **L-5**) dramatically enhanced the β-selectivity and shortened the reaction time (entries 8 and 9). The optimal conditions with the use of 4-chloro-2-trifluoroacetylphenol (**L-5**) as the ligand has been established in terms of anomeric selectivity (α:β = 1:16), yield (88%), and reaction time (2.5 h) (entry 9). Thus, striking a balance between the electronic nature of the σ-donor ligands is key to increasing the β-selectivity and shortening the reaction time. To determine if the effect of salicylaldehyde (**L-1**) and its derivatives (**L-4** and **L-5**) on the anomeric selectivity does not simply derive from incorporation of a weak acid, a control experiment was performed with 4-hydroxybenzaldehyde (**L-6**), whose acidity is comparable to that of salicylaldehyde. The desired *N*-glycosyl trichloroacetamide **11** was isolated in 63% yield with α:β = 1:3 (entry 10). This result validates that coordination of salicylaldehyde (**L-1**) and its derivatives (**L-4** and **L-5**) to palladium is important for the high stereoselectivity observed in the product.

When cationic palladium(II),[15,19] $Pd(CH_3CN)_4(BF_4)_2$ (2.5 mol %), was employed in the reaction, the desired α-*N*-glycosyl trichloroacetamide **11** was obtained in 73% yield as the major anomer (Table 3, entry 1). Thus, switching to the cationic palladium reverses the anomeric selectivity, favoring the α-anomer. Addition of 10 mol % of salicylaldehyde (**L-1**) significantly increased the α-selectivity (entry 2). Further optimization focused on the catalyst loading. Decreasing the catalyst loading to 0.5 mol % from 2.5 mol % gave 82% of **11** with α:β = 13:1 (entry 3). Lowering the catalyst further decreased the yield and the α-selectivity (entry 4). To determine if HBF_4, which may generate from the cationic palladium catalyst, is the source of catalysis, the rearrangement was performed in the presence of 2,6-di-*tert*-butylpyridine (DTBP) (5 mol %) as an acid scavenger (entry 5). In the event, the formation of α-anomer **11** from glycal imidate **10** proceeded in comparable yield and selectivity to those of entries 1−4. Switching to the more electron-withdrawing ligand, **L-4** (2-trifluoroacetylphenol), showed improved yield and α-selectivity (entry 6). A control experiment was performed with 4-hydroxybenzaldehyde (**L-6**) to determine the effect of the salicylaldehyde and its derivatives on the yield and anomeric selectivity of the rearrangement (entry 8). The desired trichloroacetamide **11** was isolated in 58% yield with α:β = 10:1. Because 4-hydroxybenzaldehyde (**L-6**) is a weak acid, it could potentially decompose the acid-sensitive glycal trichloroacetimidate starting material **10** during the course of the reaction. In contrast, salicylaldehyde (**L-1**) and its derivatives (**L-4** and **L-5**) were responsible for the high yield and α-selectivity observed in the product.

Chart 1 summarizes the result of the application of the optimized neutral palladium(II) conditions to a series of glycal trichloroacetimidates. Both **L-1** (salicylaldehyde) and **L-5** (4-chloro-2-trifluoroacetylphenol) ligands provided the desired products **12**−**16** with good β-selectivity. In general, the rearrangement was faster with the **L-5** ligand, and the glycosyl

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Scheme 2

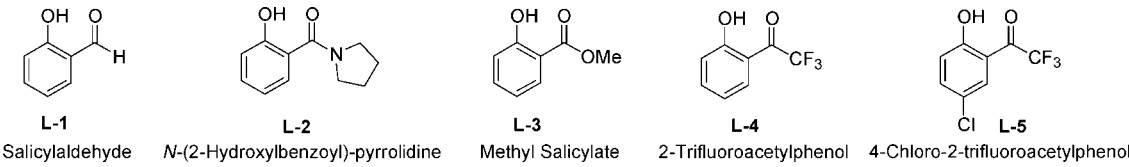
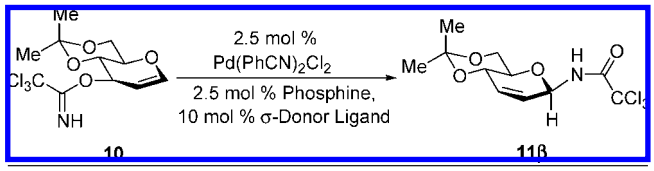


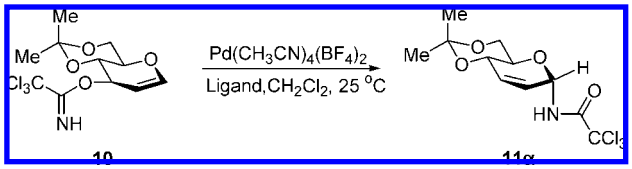
Table 2. Optimization for Stereoselective Synthesis of β-*N*-Glycosyl Trichloroacetamide with σ-Donor Ligands[a]



entry	phosphine ligand	σ-donor ligand	time, h	temp, °C	yield,[b] %	α:β[c]
1	*t*-BuX-Phos	L-1	6	25	70	1:7
2	TTMPP	L-1	4	25	86	1:9
3	TTMPP	L-1	8	0	30	1:6
4	TTMPP	L-1	2	40	75	1:4
5	none	L-1	1	25	71	1:2
6	TTMPP	L-2	24	25	82	1:8
7	TTMPP	L-3	7	25	70	1:7
8	TTMPP	L-4	2.5	25	95	1:12
9	TTMPP	L-5	2.5	25	88	1:16
10	TTMPP	L-6[d]	3	25	63	1:3

[a] All reactions were carried out in CH_2Cl_2 (0.2 M) with 2.5 mol % $Pd(PhCN)_2Cl_2$, 2.5 mol% phosphine ligand, and 10 mol % σ-donor ligand except for entry 5. [b] Isolated yield. [c] ^{1}H NMR ratio. [d] L6 = 4-hydroxybenzaldehyde.

Table 3. Cationic Pd(II)-Catalyzed Stereoselective Formation of α-*N*-Glycosyl Trichloroacetamide[a]



entry	palladium, mol %	ligand	additive	time	yield, %[b]	α:β[c]
1	2.5	none	none	45 min	73	9:1
2	2.5	10 mol % L-1	none	1 h	80	14:1
3	0.5	2 mol % L-1	none	1 h	82	13:1
4	0.1	0.4 mol % L-1	none	2 h	78	9:1
5	0.5	2 mol % L-1	DTBP	1 h	79	9:1
6	0.5	2 mol % L-4	none	45 min	93	14:1
7	0.5	2 mol % L-5	none	45 min	83	15:1
8	0.5	2 mol % L-6[d]	none	45 min	58	10:1

[a] All reactions were carried out in CH_2Cl_2 (0.2 M) with $Pd(CH_3CN)_4(BF_4)_2$ and σ-donor ligand (1:4) except for entry 1. [b] Isolated yield. [c] ^{1}H NMR ratio. [d] L6 = 4-hydroxybenzaldehyde.

trichloroacetamides were obtained with higher β-selectivity. Furthermore, these results suggest that the deactivating effect of a 4,6-acetal protecting groups on these glycal trichloroacetimidates restrict them in the tg conformations, thus limiting ionization to favor β-anomers.[20] On the other hand, glycal imidates incorporating acyclic protecting groups gave a mixture of α- and β-*N*-glycosyl trichloroacetamides such as **17** and **18**.

Under the optimized cationic palladium(II) conditions, both **L-1** (salicylaldehyde) and **L-4** (2-trifluoroacetylphenol) ligands

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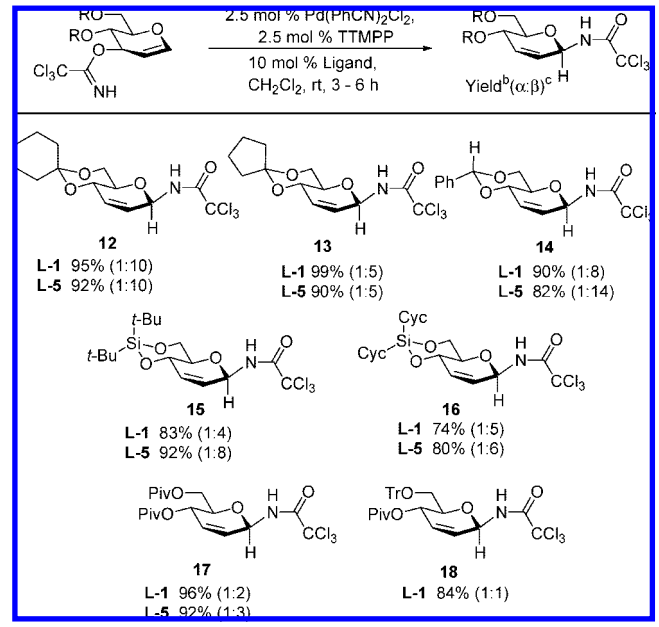
Chart 1. Synthesis of β-*N*-Glycosyl Trichloroacetamides [a–c]



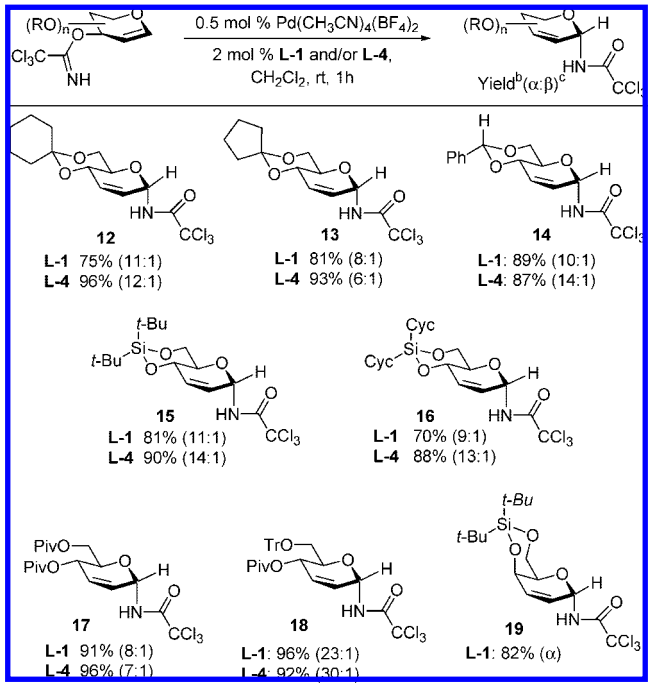
[a] All reactions were performed with 2.5 mol % $Pd(PhCN)_2Cl_2$ and 2.5 mol % of TTMPP and 10 mol % of **L-1** or **L-5** ligands. [b] Isolated yield. [c] ^{1}H NMR ratio.

provided the desired products **12**−**19** with excellent α-selectivity (Chart 2). In general, the glycosyl trichloroacetamides were obtained with higher α-selectivity when **L-4** was employed as ligand in the rearrangement. These results suggest that the cationic palladium−ligand complex was responsible for the observed α-selectivity at the anomeric center, and the nature of the protecting groups on the glycal substrates had little effect on the selectivity.

We also investigated whether the glycal imidate rearrangement could be catalyzed by a Lewis acid (Scheme 3). Accordingly, treatment of glycal imidate **10** with 0.5 mol % TMSOTf in CH_2Cl_2 only resulted in decomposition. This result suggests that the Lewis-acid-catalyzed rearrangement is intolerant of the acid-sensitive glycal imidates. Under thermal conditions, the rearrangement provided **11** in a quantitative yield. However, it took 6 h at 120 °C for the reaction to go to completion. Based on the concerted nature of the thermal [3,3]-sigmatropic rearrangement, the configuration at C(1) in **11** was assigned as the β-anomer. The ^{1}H NMR of **11** matches with that of the neutral palladium(II)-catalyzed rearrangement of **10**. The NH-resonance of β-isomer **11** appeared at δ = 6.92 ppm. In the present series of β-*N*-glycosyl trichloroacetamides, we typically found the NH-resonances at δ = 6.87−6.97 ppm.

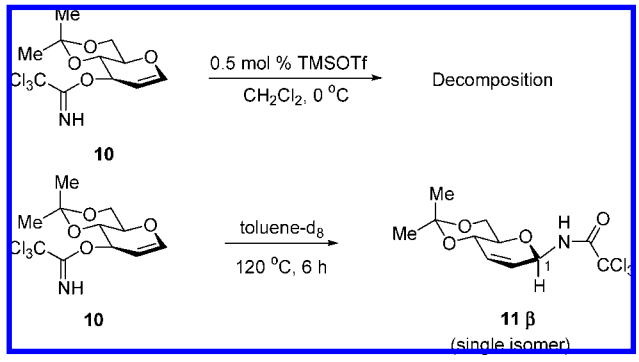
The chemical shifts of the NH proton are consistently unique for the α-anomer products. In the present series of α-*N*-glycosyl trichloroacetamides, we typically found the NH-resonances at δ = 7.15−7.26 ppm. To confirm the anomeric stereochemistry in the α-*N*-glycosyl trichloroacetamide series, α-anomer **15** was

Chart 2. Synthesis of α-*N*-Glycosyl Trichloroacetamides [a–c]

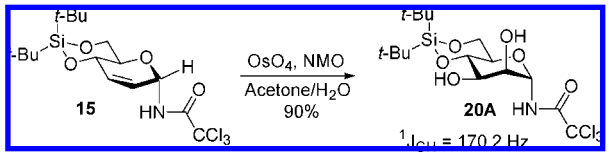


[a] All reactions were performed with 0.5 mol % $Pd(CH_3CN)_4(BF_4)_2$ and 2.0 mol % **L-1** or **L-4** ligands. [b] Isolated yield. [c] ^{1}H NMR ratio.

Scheme 3



Scheme 4



treated with OsO_4 and NMO to provide the corresponding diol **20A** (Scheme 4). The $^1J_{CH}$ coupling between the anomeric carbon of **20A** and its associated proton was measured, and $^1J_{CH}$ = 170.2 Hz. It is known that, in a standard chair conformation, *O*-glycopyranosides with a value of 173 Hz is diagnostic for an α-linkage.[21]

B. Stereoselective Synthesis of Glycosyl Ureas. During the course of our methodology studies, we became interested in the synthesis of glycosyl ureas because their functionality is increasingly recognized as a biologically relevant moiety.[22] A number of powerful tools have emerged recently for the construction of this functionality.[8,9] However, the stereoselective synthesis of α- and *β*-glycosyl ureas is still lacking. Additionally, glycosyl ureas are generally prepared in several steps starting from glycosyl azides.[8] In our methodology studies, glycosyl ureas were formed by dihydroxylation of *N*-glycosyl trichloroacetamide and subsequent treatment of the resulting diol intermediate with a base and a nitrogen nucleophile (Scheme 5). It was hypothesized that the trichloroacetamide proton could be selectively deprotonated to generate an isocyanate in situ, which would subsequently participate in the glycosyl urea formation in the presence of a nucleophilic nitrogen. In this strategy, there is no loss of stereochemical integrity at the C(1)-anomeric position, a major drawback of other methodologies.

This approach can be flawed, however, by the competing hydrolysis pathway to form the free amine at the C(1)-position,[23] which then undergoes anomerization. Determined to showcase *N*-glycosyl trichloroacetamide substrates as robust and versatile intermediates, we screened a number of bases and solvents (Table 4). Using NaH or K_2CO_3 as a base in THF resulted in no reaction (entries 1 and 2). Performing the reaction in DMF with K_2CO_3 as a base resulted in hydrolysis of the trichloroacetyl group of **23** to provide the free amine, which underwent anomerization to form *β*-anomer (entry 3). Ultimately, it was found that the softer base Cs_2CO_3 with DMF as solvent to be ideally suited to the task (entry 4). With use of *n*-butylamine as a nitrogen nucleophile, the desired α-glycosyl urea **24** was isolated in 74% yield. In contrast to other methods,[8] our approach requires only 2−3 steps for the synthesis of a α-glycosyl urea starting from α-*N*-glycosyl trichloroacetamide. Most importantly, the stereochemical integrity at the anomeric carbon remains intact.[24]

With optimized reaction conditions in hand, we set out to define the scope of this transformation. We discovered that a diverse array of primary and secondary nitrogen nucleophiles could be coupled to α-glycosyl trichloroacetamides **15** and **18** to form the corresponding α-glycosyl ureas **25**−**31** in moderate to good yields and with no anomerization (Table 5). Notably, the efficiency of this reaction is demonstrated by the ability to couple methylpiperazine and pyridylpiperazine with α-glycosyl trichloroacetamide **18** to form α-glycosyl ureas **30** and **31**, respectively (entries 6 and 7).

There are only a few examples of symmetrical urea-linked disaccharides, in which two glucopyranoside units are bound at the two anomeric positions.[5,8a] Furthermore, there are only two reports on the synthesis of unsymmetrical urea-linked disaccharides, in which the anomeric position of a glycopyranosyl donor is connected to the nonanomeric position of a glycopyranosyl acceptor.[8f,25] Encouraged by the results obtained with noncarbohydrate amines in Table 5, we decided to explore the feasibility of our method with primary and hindered amines

(21) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.

(22) Ellestad, G. A.; Cosulich, D. B.; Broschard, R. W.; Martin, J. H.; Kunstmann, M. P.; Morton, G. O.; Lancaster, J. E.; Fulmor, W.; Loevell, G. M. *J. Am. Chem. Soc.* **1978**, *100*, 2515–2524.

(23) (a) Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Tetrahedron* **1999**, *55*, 4325–4340. (b) Urabe, D.; Sugino, K.; Nishikawa, T.; Isobe, M. *Tetrahedron. Lett.* **2004**, *45*, 9405–9407.

(24) The five step non-selective method for the synthesis of glycosyl urea from α-glycosyl azide was developed by Isobe and coworkers to circumvent the unsuccessful attempt at forming the isocyanate in situ from trichloroacetamide. Ichikawa, Y.; Nishiyama, T.; Isobe, M. *Synlett* **2000**, 1253–1256.

(25) Propseri, D.; Ronchi, S.; Lay, L.; Rencurosi, A.; Russo, G. *Eur. J. Org. Chem.* **2004**, 395–405.

Scheme 5

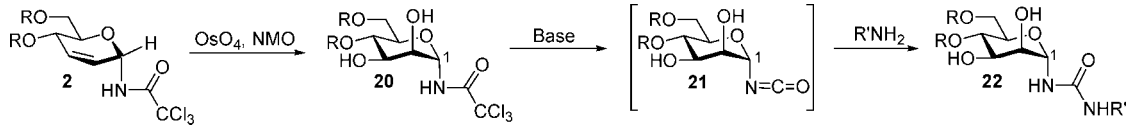
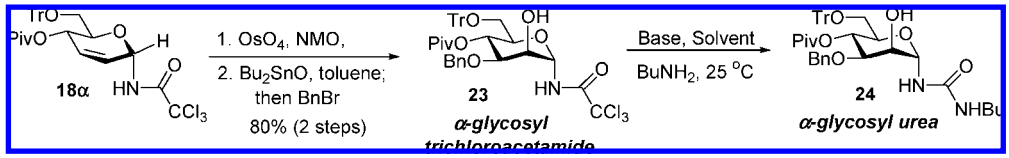
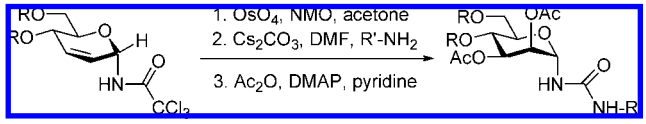


Table 4. Transformation of *N*-Glycosyl Trichloroacetamide into a Glycosyl Urea



entry	base	solvent	results
1	NaH	THF	no reaction
2	K_2CO_3	THF	no reaction
3	K_2CO_3	DMF	hydrolysis
4	Cs_2CO_3	DMF	74% yield

Table 5. Stereoselective Synthesis of α-Glycosyl Ureas[a]

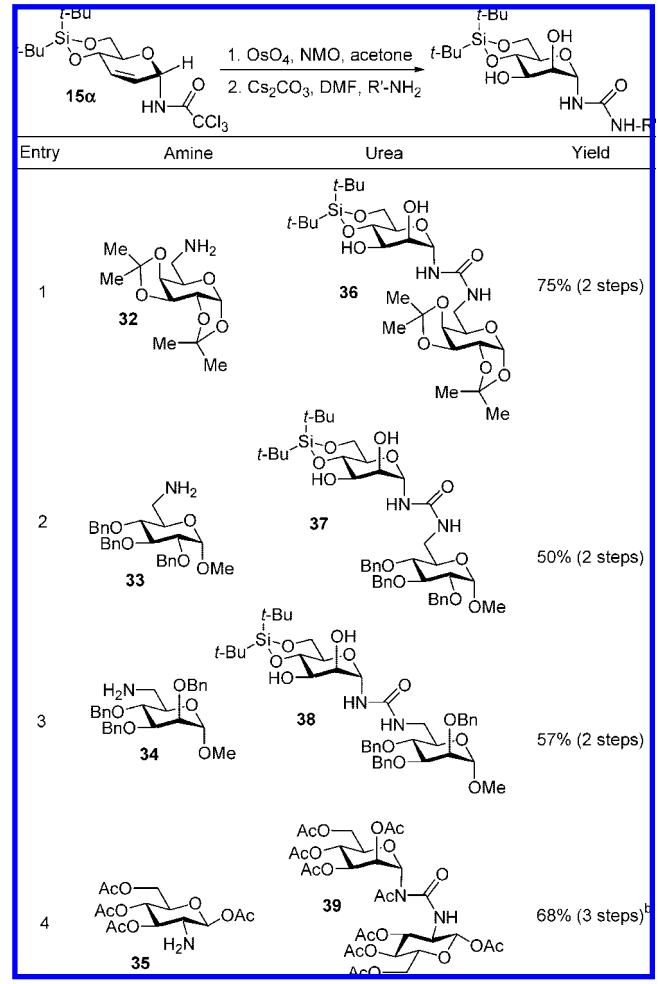


Entry	α-Trichloroacetamide	Amine	Urea	Yield[b] (3 steps)
1	**15α**	Benzylamine	**25**	50%
2	**15α**	*n*-Butylamine	**26**	58%
3	**15α**	Cyclohexylamine	**27**	59%
4	**18α**	Pyrrolidine	**28**	58%
5	**18α**	Piperidine	**29**	61%
6	**18α**	Methylpiperazine	**30**	70%
7	**18α**	Pyridylpiperazine	**31**	51%

[a] All reactions were performed in DMF at 25 °C with Cs_2CO_3 (4 equiv) and R′-NH_2 (2−3 equiv). [b] Yield included three steps.

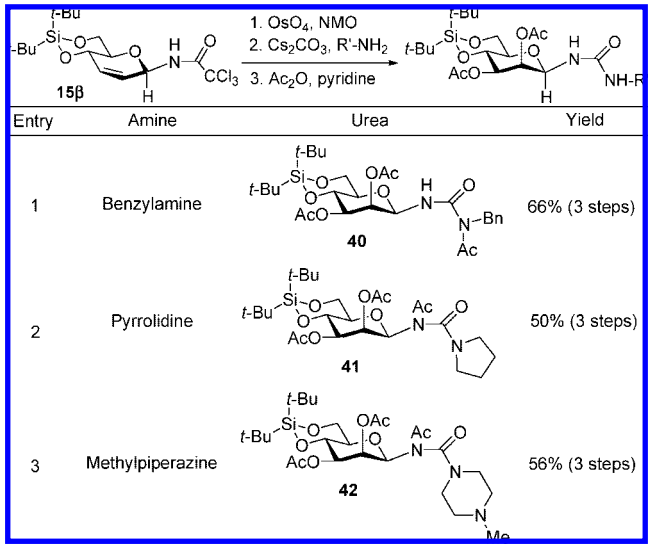
of carbohydrate nucleophiles **32**−**35** (Table 6). Gratifyingly, it was found that these carbohydrate amines are suitable nucleophiles for the preparation of various unsymmetrical urea-linked disaccharides. In order to achieve high conversion, an excess amount of carbohydrate amines (2−3 equiv) were employed in the reaction, and the unreacted amines were recovered after chromatography. The most encouraging result was discovered

Table 6. Synthesis of Unsymmetrical Urea-Linked Disaccharides[a]



[a] All reactions were performed in DMF at 25 °C with Cs_2CO_3 (4 equiv) and R′-NH_2 (2−3 equiv). [b] The polyol intermediate of **39** was acylated to ease the purification process.

Table 7. Stereoselective Synthesis of β-Glycosyl Ureas[a]



Entry	Amine	Urea	Yield
1	Benzylamine	**40**	66% (3 steps)
2	Pyrrolidine	**41**	50% (3 steps)
3	Methylpiperazine	**42**	56% (3 steps)

[a] All reactions were performed in DMF at 25 °C with Cs_2CO_3 (4 equiv) and R′-NH_2 (2−3 equiv). The diol intermediates of glycosyl ureas were acylated to ease the purification process.

when the hindered amine of tetra-*O*-acetyl glucosamine **35** was efficiently coupled with α-glycosyl trichloroacetamide **15** to form unsymmetrical urea-linked disaccharide **39** in 68% yield. In this reaction, the bis(*tert*-butylsilyl) group was replaced with the acetyl group during the course of the reaction.

These results were encouraging because they clearly showed that our methodology is amenable to most amines. We also examined this chemistry with β-*N*-glycosyl trichloroacetamides (Table 7). Under standard conditions, coupling of **15*β*** with primary and secondary amines provided the corresponding β-glycosyl ureas **40**−**42** in moderate yields.

To this point, the efficacy of transforming α- and β-glycosyl trichloroacetamides into α- and β-glycosyl ureas has been demonstrated only in the preparation of urea-linked disaccharides. The true test of the versatility of this concept is its ability to function in the synthesis of complex pseudooligosaccharides. At the same time, the synthesis of urea-linked oligosaccharides would showcase our methodology of Pd(II)-catalyzed rearrangement of glycal trichloroacetimidates. Therefore, synthesis of urea-linked trisaccharide **49** was undertaken (Scheme 6).

Preparation of urea-linked pseudotrisaccharide **49** was targeted so that we can determine its bactericidal activity as well as stability compared to other pseudodisaccharides. Under our conditions of cationic Pd(II)-catalyzed stereoselective glycosylation,[26] coupling of glycosyl trichloroacetimidate donor **43**[27] with nucleophilic acceptor **44** provided disaccharide **45** in 70% yield exclusively as α-anomer (Scheme 6). Hydrolysis of the acetyl group followed by treatment of the resulting allylic alcohol intermediate with trichloroacetonitrile and DBU afforded the corresponding disaccharide trichloroacetimidate **46** in 91% yield over two steps. With **46** in hand, the next step is to employ our method of Pd(II)-catalyzed glycal imidate rearrangement. The desired disaccharide trichloroacetamide **47** was isolated in 91% yield with an anomeric ratio of 5:1, favoring the α-anomer. Subsequent dihydroxylation of **47** followed by coupling of the resulting diol **48** with carbohydrate primary amine **32** provided urea-linked trisaccharide **49** in 68% yield and with no epimerization of the anomeric C−N bond.

Conclusions

In summary, a novel method for palladium(II)-catalyzed stereoselective formation of α- and β-*N*-glycosyl trichloroacetamides has been developed. The α- and β-selectivity at the anomeric carbon of *N*-glycosyl trichloroacetamides depends on the nature of the palladium−ligand catalyst. While the cationic palladium−**L-4** (2-trifluoroacetylphenol) complex promotes the α-selectivity, the neutral palladium−TTMPP-**L-5** (4-fluoro-2-trifluoroacetylphenol) complex favors the β-selectivity. Because of its substrate tolerance and mild conditions, this palladium method is applicable to a wide range of glycal imidates. The resulting α- and β-*N*-glycosyl trichloroacetamides were further coupled with a diverse array of primary and hindered secondary nitrogen nucleophiles to provide the corresponding glycosyl ureas in moderate to good yields and with no loss of stereochemical integrity at the anomeric carbon. We have further demonstrated the utility of *N*-glycosyl trichloroacetamides as robust and versatile intermediates in the synthesis of unsymmetrical urea-linked disaccharides and trisaccharide. These glycosyl ureas will be evaluated for their antibacterial activity.

Experimental Section

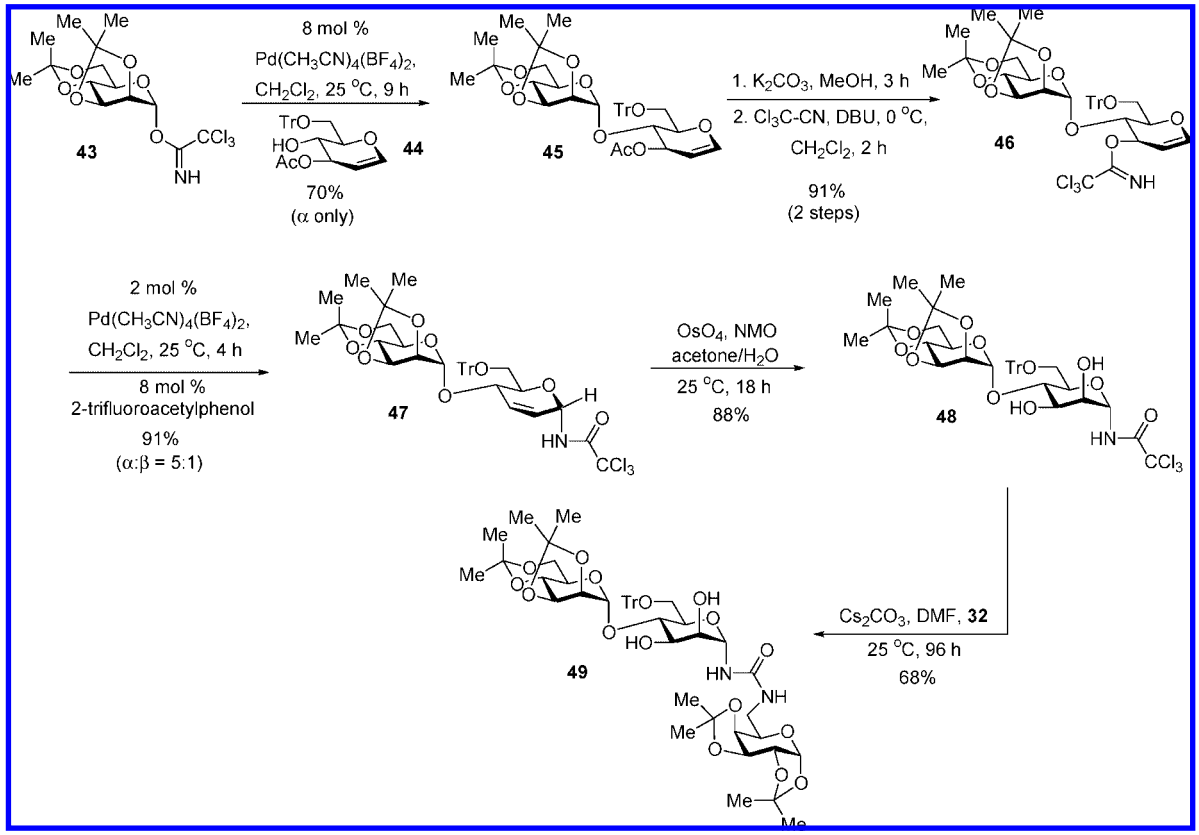
Representative experimental procedures are listed here. Full experimental details and spectral data for all new compounds can be found within the Supporting Information.

Preparation of *β*-*N*-Glycosyl Trichloroacetamide 11*β* with L-5 (4-chloro-2-trifluoroacetylphenol) as Ligand. A 10 mL oven-dried Schlenk flask was charged with $Pd(PhCN)_2Cl_2$ (2.9 mg, 0.0075 mmol, 2.5 mol%), TTMPP (4.0 mg, 0.0075 mmol, 2.5% mol), and CH_2Cl_2 (1.5 mL). The solution was stirred at 25 °C for 2 h, and **L-5** (6.7 mg, 0.03 mmol, 10 mol%) was then added. The resulting mixture was stirred for 1 h, and glucal imidate **10** (99 mg, 0.3 mmol, 1 equiv) was added. The reaction mixture was stirred for 90 min, diluted with benzene (2 mL), concentrated to about 1 mL, and purified by silica gel flash chromatography (8/1 → 4/1, hexane/ethyl acetate) to give **11** (88 mg, 88%, α:β = 1:16) as a white solid: mp = 121−122 °C; R_f = 0.33 (4/1, hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.92 (d, J = 8.5 Hz, 1H, NH), 6.10 (d, J = 10.0 Hz, 1H, H2), 5.97 (d, J = 7.0 Hz, 1H, H1), 5.64 (d, J = 10.5 Hz, 1H, H3), 4.33 (d, J = 7.5 Hz, 1H, H4), 3.92 (dd, J = 10.5, 5.5 Hz, 1H, H6), 3.79 (t, J = 10.5 Hz, 1H, H6), 3.61 (ddd, J = 10.5, 7.5, 5.5, 1H, H5), 1.51 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 161.3, 133.2, 125.8, 100.0, 92.0, 77.7, 72.3, 66.8, 62.4, 29.1, 19.0; IR (film, cm^{-1}): υ = 3329, 2923, 1713, 1512, 1095; HRMS (ESI): calcd for $C_{11}H_{14}Cl_3N_1O_4Na$ [M + Na] 351.9881; found: 351.9882.

Preparation of α-*N*-Glycosyl Trichloroacetamide 11 with L-4 (2-trifluoroacetylphenol) as Ligand. A 10 mL oven-dried Schlenk flask was charged with glucal imidate **10** (99 mg, 0.3 mmol, 1 equiv) and CH_2Cl_2 (1.0 mL). A preformed solution of $Pd(CH_3CN)_4(BF_4)_2$ (0.67 mg, 0.0015 mmol, 0.5 mol%) and **L-4** (1.14 mg, 0.006 mmol, 2.0 mol%) in CH_2Cl_2 (0.5 mL), which had been stirring at 25 °C for 2 h, was added. The resulting mixture was stirred at 25 °C for 45 min, diluted with benzene (2 mL), concentrated to about 1 mL, and purified by silica gel flash chromatography (8/1 → 4/1, hexane/ethyl acetate) to give **11** (92.2 mg, 93%, α:β = 14:1) as a white solid: mp = 125−128 °C; R_f= 0.38 (4/1, hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.22 (bs, 1H, NH), 6.18 (d, J = 10.0 Hz, 1H, H2), 5.81 (dd, J = 9.0, 2.0 Hz, 1H, H1), 5.72 (dt, J = 10.0, 2.5 Hz, 1H, H3), 4.25 (d, J = 9.0 Hz, 1H, H4), 3.92 (dd, J = 11.0, 5.5 Hz, 1H, H6), 3.80 (t, J = 11.0 Hz, 1H, H6), 3.47 (ddd, J = 11.0, 9.0, 5.5, 1H, H5),

(26) Yang, J.; Cooper-Vanosdell, C.; Mensah, E. A.; Nguyen, H. M. *J. Org. Chem.* **2008**, *73*, 794–800.
(27) Drew, K. N.; Gross, P. H. *J. Org. Chem.* **1991**, *56*, 509–513.

Scheme 6



1.52 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 161.4, 134.0, 124.6, 100.1, 92.2, 74.5, 72.3, 67.0, 66.7, 62.9, 29.1, 18.9; IR (film, cm^{-1}): υ = 3329, 2923, 1710, 1498, 1099, 1038; HRMS (ESI): calcd for $C_{11}H_{14}Cl_3N_1O_4Na$ [M + Na] 351.9881; found: 351.9882.

Preparation of α-*N*-Glycosyl Urea 24. Compound **23** (75 mg, 0.10 mmol, 1 equiv) was added to a Schlenk flask as a solution in THF, and the THF was removed *in vacuo*. The alcohol was subsequently azeotroped with toluene (3 × 1.5 mL). Cesium carbonate (132 mg, 0.40 mmol, 4 equiv) was added to the flask followed by *n*-butylamine (79 μL, 0.6 mmol, 6 equiv) and *N*,*N*-dimethylformamide (2 mL). The cloudy solution was stirred at 25 °C for 20 h. This heterogeneous mixture was poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) with an ethyl acetate wash of the reaction flask. The crude product was extracted with ethyl acetate (5 × 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (2/1, hexane/ethyl acetate) to give **24** (51 mg, 74%). R_f= 0.31 (3/1, hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ = 7.50−7.15 (m, 20H), 5.07 (t, J = 10 Hz, 1H), 4.56 (dd, J = 26, 12 Hz, 2H), 4.17 (s, 1H), 4.04 (d, J = 2 Hz, 1H), 3.53−3.47 (m, 2H), 3.22 (dd, J = 10, 7 Hz, 1H), 3.18−3.12 (m, 1H), 2.93 (d, J = 10 Hz, 1H), 2.81−2.75 (m, 1H), 2.42 (bs, 1H), 1.62−1.49 (m, 2H), 1.46−1.36 (m, 2H), 0.93 (t, J = 7 Hz, 3H), 0.89 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ = 144.0, 128.8, 128.5, 128.0, 127.8, 126.9, 87.6, 80.2, 75.8, 71.8, 69.1, 67.9, 63.2, 45.4, 32.5, 2639, 20.6, 14.1; IR (film, cm^{-1}): υ = 2957 (s), 2929 (s), 2871 (s), 1734 (vs), 1491 (m), 1478 (m), 1449 (s), 1279 (m), 1153 (vs), 1106 (s), 1062 (s), 1037 (s), 699 (vs); HRMS (ESI): calcd for $C_{42}H_{50}N_2NaO_7$ (M + Na) 717.3516; found: 717.3526.

Preparation of α-*N*-Glycosyl Urea 25. Diol **20A** (72 mg, 0.15 mmol, 1 equiv) was added to a Schlenk flask as a solution in THF, and the THF was removed *in vacuo*. The diol was subsequently azeotroped with toluene (3 × 1.5 mL). Cesium carbonate (195 mg, 0.6 mmol, 4 equiv) was added to the flask followed by benzyl amine (98 μL, 0.9 mmol, 6 equiv) and *N*,*N*-dimethylformamide (3 mL). The cloudy solution was stirred at 25 °C for 20 h. This heterogeneous mixture was poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) with an ethyl acetate wash of the reaction flask. The crude product was extracted with ethyl acetate (5 × 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. To a scintillation vial the crude urea was combined with pyridine (1.5 mL), acetic anhydride (200 μL, 1.8 mmol, 6 equiv), and one crystal of *N*,*N*-dimethylaminopyridine. The solution was stirred at 25 °C for 21 h and then concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (1/1, hexane/ethyl acetate) to give **25** (44 mg, 55%). R_f= 0.65 (1/1, hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ = 7.35−7.20 (m, 5H), 5.49 (d, J = 9.5 Hz, 1H), 5.32 (d, J = 2.5 Hz, 1H), 5.21 (d, J = 9.5 Hz, 1H), 4.97 (dd, J = 9.5, 4.0 Hz, 1H), 4.91−4.86 (m, 1H), 4.32 (ddd, J = 16.0, 10.0, 4.5 Hz, 2H), 4.17 (dd, J = 10.0, 5.0 Hz, 1H), 3.99 (t, J = 9.5 Hz, 1H), 3.85 (t, J = 10.0 Hz, 1H), 3.56 (td, J = 10.0, 5.0 Hz, 1H), 2.11 (s, 3H), 2.01 (s, 3H), 1.02 (s, 9H), 0.95 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ = 170.2, 170.0, 155.8, 138.2, 128.7, 127.6, 127.5, 78.1, 73.4, 72.7, 71.5, 71.0, 66.1, 44.6, 27.3, 26.9, 22.6, 20.8, 20.6, 19.9; IR (film, cm^{-1}): υ = 3347 (br, w), 2834 (m), 2893 (w), 2860 (m), 1753 (s), 1675 (m), 1645 (s), 1560 (s), 1236 (s), 1236 (s), 1077 (s); HRMS (ESI): calcd for $C_{26}H_{40}N_2O_8SiNa$ (M + Na) 559.2446; found: 559.2411.

Preparation of Urea-Linked Pseudodisaccharide 36. Diol **20A** (72 mg, 0.15 mmol, 1.0 equiv) was added to a Schlenk flask as a solution in THF, and the THF was removed *in vacuo*. The diol was subsequently azeotroped with toluene (3 × 1.5 mL). Cesium carbonate (146 mg, 0.45 mmol, 3.0 equiv) was added to the flask followed by (−)-6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[28] (106 mg, 0.41 mmol, 2.7 equiv) and *N*,*N*-dimethylformamide (2.1 mL). The cloudy solution was stirred at 25 °C for 96 h. This heterogeneous mixture was poured into a

(28) Streicher, B.; Wunsch, B. *Carbohydr. Res.* **2003**, *338*, 2375–2385.

saturated aqueous solution of $NaHCO_3$ (30 mL) with an ethyl acetate wash of the reaction flask. The crude product was extracted with ethyl acetate (5 × 30 mL). This organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (1/9, hexane/ethyl acetate) to give **36** (68 mg, 75%) as a white solid: mp = 126 °C; R_f= 0.27 (1/1, hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ = 6.11 (d, J = 9.5 Hz, 1H), 5.48 (d, J = 5.0 Hz, 1H), 5.32 (dd, J = 7.5, 4.0 Hz, 1H), 5.16 (d, J = 9.5 Hz, 1H), 4.56 (dd, J = 8.0, 2.0 Hz, 1H), 4.27 (dd, J = 5.0, 2.5 Hz, 1H), 4.17 (dd, J = 7.5, 1.0 Hz, 1H), 4.13 (dd, J = 10.0, 5.0, Hz, 1H), 3.96 (apparent s, 1H), 3.90 (t, J = 9.0 Hz, 1H), 3.88−3.82 (m, 2H), 3.63 (apparent d, J = 9.0 Hz, 1H), 3.54−3.40 (m, 3H), 3.25−3.17 (m, 1H), 3.06 (apparent s, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.01 (s, 9H), 0.95 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ = 156.9, 109.5, 108.9, 96.3, 79.4, 74.6, 74.3, 71.7, 71.6, 70.8, 70.7, 67.1, 66.1, 40.8, 27.5, 27.0, 26.1, 26.0, 25.1, 24.4, 22.6, 20.0; IR (film, cm^{-1}): υ = 3387 (br, m), 2964 (m), 2934 (s), 2897 (m), 2860 (s), 1661 (m), 1553 (m), 1473 (w), 1384 (m), 1212 (m), 1071 (m); HRMS (ESI): calcd for $C_{27}H_{48}N_2O_{11}Si$ Na (M + Na) 627.2920; found: 627.2889.

Preparation of Urea-Linked Pseudotrisaccharide 49. Diol **48** (77 mg, 0.095 mmol, 1.0 equiv) was added to a Schlenk flask as a solution in THF, and the THF was removed *in vacuo*. The diol was subsequently azeotroped with toluene (3 × 1.5 mL). Cesium carbonate (vaccuum-dried at 100 °C for 12 h) (124 mg, 0.380 mmol, 4.0 equiv) was added to the flask followed by (−)-6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[28] (99 mg, 0.380 mmol, 4.0 equiv) and *N*,*N*-dimethylformamide (1.4 mL). The cloudy solution was stirred at 25 °C for 96 h. This heterogeneous mixture was poured into a saturated aqueous solution of $NaHCO_3$ (30 mL) with an ethyl acetate wash of the reaction flask. The crude product was extracted with ethyl acetate (5 × 30 mL). This organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (1/1, hexane/ethyl acetate) to give **49** (61 mg, 68%). R_f = 0.12 (1/1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ = 7.49−7.19 (m, 15H), 5.97 (bs, 1H), 5.76 (bs, 1H), 5.34−5.28 (m, 1H), 5.32 (s, 1H), 5.13 (bs, 1H), 4.61−4.54 (m, 2H), 4.47 (d, J = 5.5 Hz, 1H), 4.03−3.95 (m, 2H), 3.95−3.89 (m, 1H), 3.86 (t, J = 4 Hz, 1H), 3.84−3.78 (m, 3H), 3.69 (dd, J = 7, 3.5 Hz, 1H), 3.51 (dd, J = 10.5, 3 Hz, 1H), 3.47−3.27 (m, 5H), 1.45 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.29 (s, 6H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ = 158.75, 143.85, 128.78, 127.80, 126.93, 112.61, 109.44, 109.02, 108.77, 105.92, 95.17, 86.82, 85.30, 80.91, 79.43, 73.03, 72.49, 71.29, 70.69, 70.53, 70.33, 66.74, 62.66, 29.68, 26.71, 25.99, 25.89, 25.17, 24.94, 24.60, 24.49; IR (film, cm^{-1}): υ = 3378 (br, s), 2986 (s), 2931 (s), 1666 (s), 1549 (m), 1449 (m), 1381 (s), 1256 (m), 1211 (s), 1070 (vs); HRMS (ESI): calcd for $C_{50}H_{64}N_2NaO_{16}$ (M + Na) 971.4148; found: 971.4186.

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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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