JOC Article

# Palladium-Controlled β-Selective Glycosylation in the Absence of the C(2)-Ester Participatory Group

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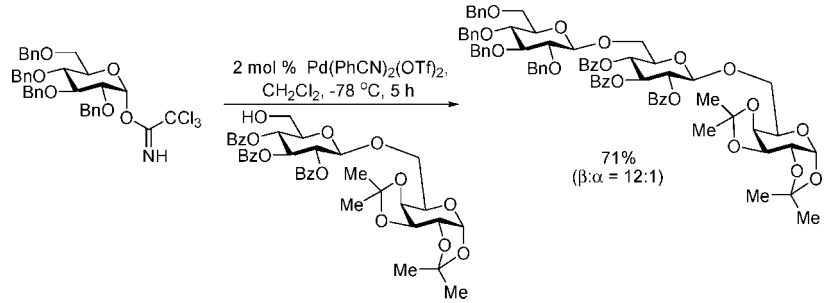


The development of a new glycosylation method for the stereoselective synthesis of β-glycosides in the absence of the traditional C(2)-ester neighboring group effect is described. This process relies on the ability of the cationic palladium catalyst, $Pd(PhCN)_2(OTf)_2$ generated in situ from $Pd(PhCN)_2Cl_2$ and AgOTf, to direct β-selectivity. The new glycosylation reaction is highly β-selective and proceeds under mild conditions with 1−2 mol % of catalyst loading. This β-glycosylation method has been applied to a number of glucose donors with benzyl, allyl, and *p*-methoxybenzyl groups incorporated at the C(2)-position as well as tribenzylated xylose and quinovose donors to prepare various disaccharides and trisaccharides with good to excellent β-selectivity. Mechanistic studies suggest that the major operative pathway is likely to proceed via a seven-membered ring intermediate, wherein the cationic palladium complex coordinates to both the C(1)-imidate nitrogen and C(2)-oxygen of the trichloroacetimidate donor. Formation of this seven-membered ring intermediate directs the selectivity, leading to the formation of β-glycosides.

## Introduction

On the surface, the stereoselective synthesis of β-glycosides appears to be a straightforward task due to the effect of traditional C(2)-neighboring group participation.[1] Ester functionalities are often employed as participatory groups at the C(2)-positions of glycosyl donors. However, the reactivity of glycosyl donors incorporating C(2)-ester functionality is significantly decreased within many glycosylation methods.[2] Thus, prolonged reaction time is often required in order to achieve efficient coupling.[3] This popular approach can also suffer from the competitive formation of ortho ester.[4] Furthermore, if the glycosylation is performed under basic conditions, the C(2)-acyl functionality can migrate to both the C(1)-position of glycosyl donors as well as the reactive sites of the nucleophilic acceptors.[5] To avoid such problems, Demchenko and co-workers have recently reported the stereoselective synthesis of β-glycosides utilizing C(2)-picolyl moiety as a novel neighboring participatory group.[6] Crich and co-workers have also reported the use of a 3,4-*O*-bisacetal system as well as a *trans*-2,3-*O*-carbonate group to influence β-glycosylation.[7]

(1) (a) Nukada, T.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291–13295. (b) Barresi, F.; Hindsgaul, O. *J. Carbohydr. Chem.* **1995**, *14*, 1043. (c) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123. (d) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed.* **1980**, *19*, 731–732.

(2) (a) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068–6070. (b) Fraser-Reid, B.; Merritt, J. R.; Handlon, A. L.; Andrews, C. W. *Pure Appl. Chem.* **1993**, *65*, 779–786.

(3) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531.

(4) (a) Kunz, H.; Harreus, A. *Liebigs Ann. Chem.* **1982**, 41. (b) Sato, S.; Nunomura, S.; Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *33*, 4097. (c) Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064. (d) Crich, D.; Dai, Z.; Gastaldi, S. *J. Org. Chem.* **1999**, *64*, 5224–5229.

(5) Yu, H.; Ensley, H. E. *Tetrahedron Lett.* **2003**, *4*, 9363–9366.

(6) Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7123–7126.

(7) (a) Crich, D.; Subramanian, V.; Hutton, T. K. *Tetrahedron* **2007**, *63*, 5042–5049. (b) Crich, D.; Jayalath, P. *J. Org. Chem.* **2005**, *70*, 7252–7259.



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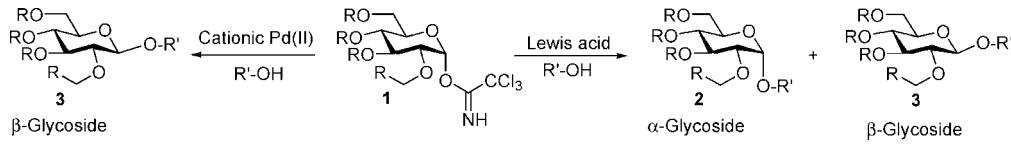
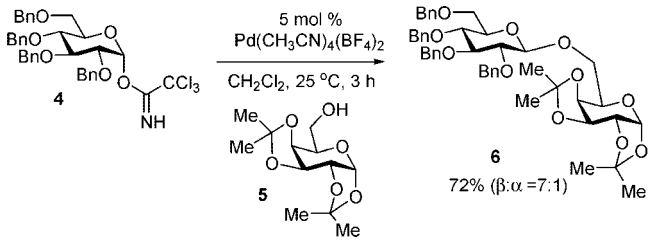
**SCHEME 1**




**SCHEME 2**



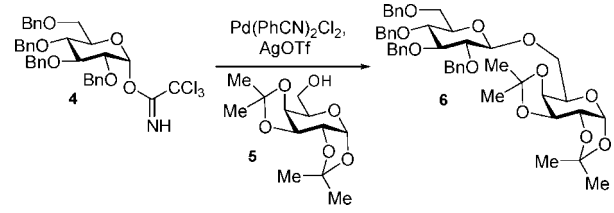

On the other hand, ether protecting groups at the C(2)-position of glycosyl donors have been explored in many glycosylation methods (e.g., glycosyl trichloroacetimidate **1**) because they enhance the reactivity of glycosyl donors (Scheme 1). However, since these C(2)-ether protected glycosyl donors appear to go through an oxocarbenium intermediate, a mixture of α- and β-glycoside products are often formed in the reaction. There are few reports on the use of nitrile solvent to improve the β-selectivity when a glycosyl donor bearing a nonparticipatory group at the C(2)-position is employed in the glycosylation reaction.[8]

Our strategy for β-glycosylation is to exploit the ability of cationic palladium catalyst to direct β-glycosylation through coordinating to both the imidate nitrogen and C(2)-oxygen of glycosyl trichloroacetimidate donors (Scheme 1). We report herein a novel method of cationic palladium controlled β-glycosylation in the absence of the traditional C(2)-ester neighboring group effect. Due to mild reaction conditions with the anomeric selectivity controlled by the nature of the cationic palladium complex, this strategy represents a promising method for constructing β-glycoside products.

## Results and Discussion

Initial studies were performed with 2,3,4,6-tetra-*O*-benzyl-D-glycopyranosyl trichloroacetimidate **4**[9] as the glycosyl donor and 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **5** as the nucleophilic acceptor.[10] Upon treatment of both coupling partners **4** and **5** with 5 mol % of commercially available cationic Pd(II) species, $Pd(CH_3CN)_4(BF_4)_2$, in $CH_2Cl_2$ at 25 °C for 3 h, the desired disaccharide **6** was isolated in 72% yield with β:α = 7:1 (Scheme 2). This result was encouraging because it clearly showed that the cationic Pd(II) catalyst could direct β-glycosylation with the C(2)-benzyl protected donor to provide the desired glycoside with good stereoselectivity.

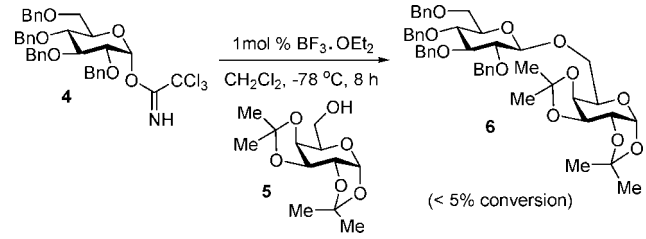
**TABLE 1. $Pd(PhCN)_2(OTf)_2$-Controlled β-Selective Glycosylation**[a]




| entry | palladium, mol % | AgOTf, mol % | additive | temp, °C | time | yield,[b] % | β:α[c] |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 4 | none | 25 | 15 min | 98 | 1:1 |
| 2 | 1 | 2 | none | 25 | 15 min | 96 | 1:1 |
| 3 | 1 | 2 | none | 0 | 30 min | 83 | 1:1 |
| 4 | 1 | 2 | none | −78 | 1 h | 87 | 10:1 |
| 5 | 1 | 2 | DTBP | −78 | 1 h | 85 | 10:1 |
| 6 | 1 | none | none | −78 | 8 h | <1 | |
| 7 | none | 2 | none | −78 | 5 h | <1 | |

[a] All reactions were carried out in $CH_2Cl_2$ (0.15 M) with AgOTf and $Pd(PhCN)_2Cl_2$. [b] Isolated yield. [c] $^1H$ NMR ratio.

**SCHEME 3**




Although the above conditions provide disaccharide **6** in good yield with a good level of β-selectivity, the cationic palladium(II) species, $Pd(CH_3CN)_4(BF_4)_2$, is relatively expensive, and at least 5 mol % of the catalyst is required for the reaction to go to completion. Thus, an ongoing goal in our group has been the development of stereoselective glycosylation reactions that utilize more reactive palladium catalysts.[11] Our approach to this problem is to carefully look at the nature of counterions on cationic Pd(II) complexes. It is known that a weakly coordinating counterion can increase catalyst activity.[12] With this hypothesis in mind, we investigated the use of cationic $Pd(PhCN)_2(OTf)_2$, generated in situ from neutral $Pd(PhCN)_2Cl_2$ and AgOTf. We choose to use AgOTf because it is easier to handle than other silver salts.

Coupling of nucleophilic acceptor **5** with trichloroacetimidate **4** in the presence of a preformed solution of 2 mol % of $Pd(PhCN)_2Cl_2$ and 4 mol % of AgOTf at 25 °C provided the desired disaccharide **6** in 98% yield as a 1:1 mixture of α- and β-isomers (Table 1, entry 1). Decreasing the catalyst loading to 1 mol % still maintained the yield. However, disaccharide **6** was still isolated as a mixture of α- and β-isomers (entry 2).

(8) (a) Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *47*, 9985–9992. (b) Marra, A.; Esnault, J.; Veyrieres, A.; Sinary, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354–6360. (c) Crich, D.; Patel, M. *Carbohydr. Res.* **2006**, *341*, 1467–1475.

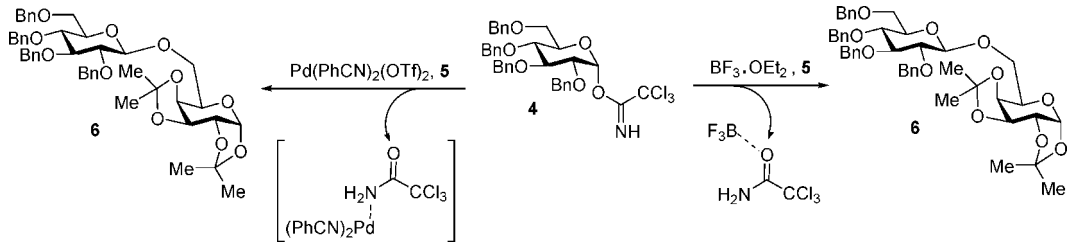
(9) (a) Zhang, J.; Yergey, A.; Kowalak, J.; Kovac, P. *Tetrahedron* **1998**, *54*, 11783–11792. (b) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481–1484. (c) Nakanishi, N.; Nagafuchi, Y.; Koizumi, K. *J. Carbohydr. Chem.* **1994**, *13*, 981–990. (d) Rathore, H.; Hashimoto, T.; Igarashi, K.; Nukaya, H.; Fullerton, D. *Tetrahedron* **1985**, *41*, 5427–5438. (e) Schmidt, R. R.; Michel, J. *Tetrahedron. Lett.* **1984**, *25*, 821–824.

(10) Yang, J.; Cooper-Vanosdell, C.; Mensah, E. A.; Nguyen, H. M. *J. Org. Chem.* **2008**, *73*, 794–800.

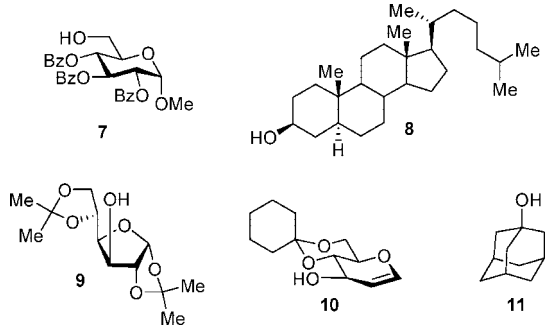
(11) (a) Schuff, B. P.; Mercer, G. J.; Nguyen, H. M. *Org. Lett.* **2007**, *9*, 3173–3176. (b) Mercer, G. J; Yang, J.; McKay, M. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2008**, *130*, 11210–11218.

(12) (a) Reed, C. A. *Acc. Chem. Res.* **1998**, *31*, 133–139. (b) Mecking, S. *Coord. Chem. Rev.* **2000**, *203*, 325–351.

**SCHEME 4**




**SCHEME 5**

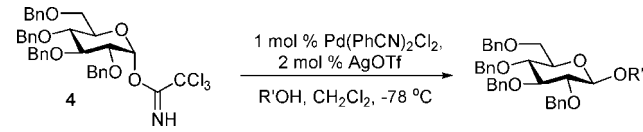


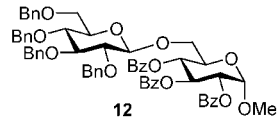
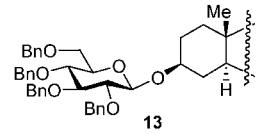
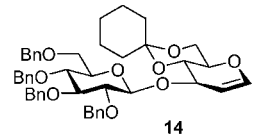
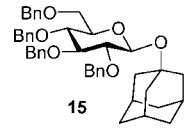

Lowering the reaction temperature to 0 °C did not have any effect on the outcome of the reaction (entry 3). Since the glycosylation reaction was complete within 30 min at 0 and 25 °C, we decided to lower the reaction temperature further to −78 °C. We were surprised to find that the $\beta$-selectivity was significantly increased at −78 °C (entry 4). In this event, disaccharide **6** was isolated in 87% yield with $\beta$:$\alpha$ = 10:1. The increase in $\beta$-selectivity from 1:1 to 10:1 observed upon cooling the reaction mixture from 0 to −78 °C suggests different mechanisms for this glycosylation process. At 0 °C, the reaction appears to go through an oxocarbenium intermediate, resulting in a mixture of $\alpha$- and $\beta$-isomers **6**. In contrast, the reaction is likely to go through an $S_N2$ displacement at − 78 °C wherein glycosyl acceptor **5** selectively approaches the $\beta$-face of trichloroacetimidate **4**, leading to the formation of $\beta$-glycoside **6**.

To determine if triflic acid, which may be generated from $Pd(PhCN)_2(OTf)_2$, is the source of catalysis, the glycosylation was performed in the presence of 2,6-di-*tert*-butylpyridine (DTBP) (10 mol %) as an acid scavenger (Table 1, entry 5). In this experiment, the desired disaccharide **6** was isolated in comparable yield and selectivity to that of entry 4. A similar glycosylation was attempted with neutral Pd(II) species, $Pd(PhCN)_2Cl_2$ (entry 6); however, less than 1% conversion was observed in the reaction. Since a stoichiometric amount of AgOTf has been used to activate trichloroacetimidate,[13] a control experiment was performed to determine if trichloroacetimidate **4** was indeed activated by 2 mol % of AgOTf at −78 °C (entry 7). Less than 1% yield of disaccharide **6** was detected from this experiment. We also investigated whether $Pd(PhCN)_2(OTf)_2$ could activate the $\beta$-isomer of trichloroacetimidate **4**, and less than 1% conversion was observed in the reaction at −78 °C.

Overall, $Pd(PhCN)_2(OTf)_2$ provided disaccharide **6** with higher yield and $\beta$-selectivity than that of $Pd(CH_3CN)_4(BF_4)_2$. In addition, the coupling process requires only 1 mol % of $Pd(PhCN)_2(OTf)_2$ in comparison to 5 mol % with

**TABLE 2. $\beta$-Selective Glycosylation with C(2)-Benzyl Glucose Donors[a]**




| Entry | R'OH | Disaccharides | Yield[b] | β:α[c] |
|---|---|---|---|---|
| 1 | 7 |  12 | 83% | β only |
| 2 | 8 |  13 | 85% | 15:1 |
| 3 | 10 |  14 | 77% | β only |
| 4 | 11 |  15 | 80% | β only |

[a] All reactions were performed in $CH_2Cl_2$ (0.15 M) with 1 mol % of $Pd(PhCN)_2Cl_2$ and 2 mol % of AgOTf for 1−3 h. [b] Isolated yield. [c] $^1H$ NMR ratio.

$Pd(CH_3CN)_4(BF_4)_2$. Compared to other glycosylation procedures utilizing trichloroacetimidate **4** as glycosyl donor, higher $\beta$-selectivity and lower catalyst loading were observed with use of $Pd(PhCN)_2(OTf)_2$ as the activator. For example, disaccharide **6** was obtained in 45% yield as a mixture of $\alpha$- and $\beta$-isomers with use of $LiClO_4$ as a promoter.[14] On the other hand, with use of LiOTf as the catalyst, disaccharide **6** was obtained in 77% yield as a 1:1 mixture of $\alpha$- and $\beta$-isomers.[15] When a moisture-stable activating reagent, $Yb(OTf)_3$, was employed in the glycosylation, disaccharide **6** was isolated in 90% as a 2:1 mixture of $\alpha$- and $\beta$-isomers.[16] With use of traditional Lewis acid, TMSOTf, as an activator, disaccharide **6** was obtained in 71% yield as a 4:1 mixture of $\alpha$- and $\beta$-isomers.[17] Recently,

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

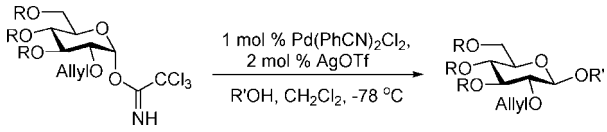
(14) Waldmann, H.; Bohm, G.; Schmid, U. *Angew. Chem., Int. Ed.* **1994**, *33*, 1944–1946.

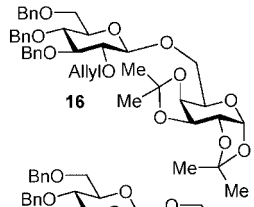
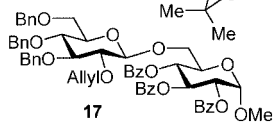
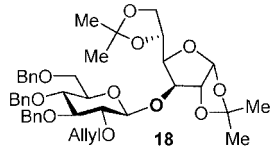
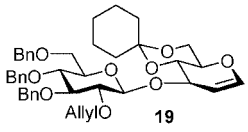
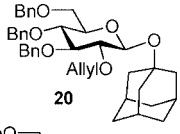
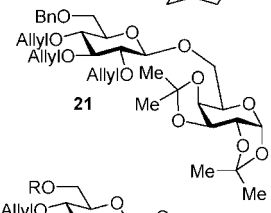
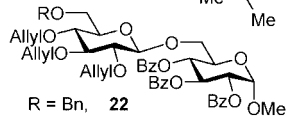
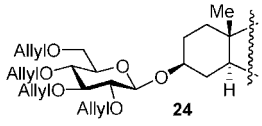
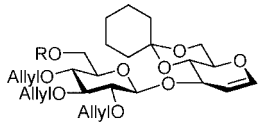
(15) Lubineau, A.; Drouillat, B. *J. Carbohydr. Chem.* **1997**, *16*, 1179–1186.

(16) Adinolfi, M.; Iadonisi, A.; Ravida, A. *Synlett* **2006**, 583–586.

(17) Meloncelli, P. J.; Williams, T. M.; Hartmann, P. E.; Stick, R. V. *Carbohydr. Res.* **2007**, *342*, 1793–1804.

**TABLE 3.** ***β*-Selective Glycosylation with C(2)-Allyl Glucose Donors**[a]

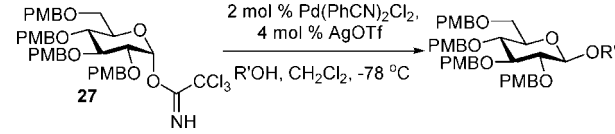


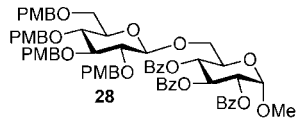
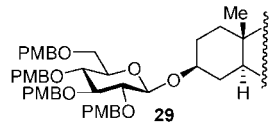
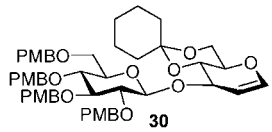
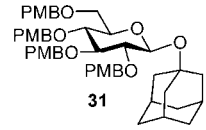

| Entry | R'OH | Disaccharides | Yield[b] | β:α[c] |
|---|---|---|---|---|
| 1 | **5** |  **16** | 99% | 13:1 |
| 2 | **7** |  **17** | 73% | β only |
| 3 | **9** |  **18** | 80% | 6:1 |
| 4 | **10** |  **19** | 82% | β only |
| 5 | **11** |  **20** | 84% | 15:1 |
| 6 | **5** |  **21** | 97% | 13:1 |
| 7 | **7** |  R = Bn, **22**<br>R = Allyl, **23** | **(22)** 74%<br>**(23)** 72% | 13:1<br>11:1 |
| 8 | **8** |  **24** | 81% | 10:1 |
| 9 | **10** |  R = Bn, **25**<br>R = Allyl, **26** | **(25)** 62%<br>**(26)** 67% | β only<br>15:1 |

[a] All reactions were performed in $CH_2Cl_2$ (0.15 M) with 1 mol % of $Pd(PhCN)_2Cl_2$ and 2 mol % of AgOTf. [b] Isolated yield. [c] $^1H$ NMR ratio.

Iadonisi and co-workers reported the use of $Sm(OTf)_3$ to activate glycosyl trichloroacetimidate **4**.[18] Although the yield and *β*-selectivity of the desired product **6** under the $Sm(OTf)_3$ conditions were comparable to those under the $Pd(PhCN)_2(OTf)_2$ conditions, the glycosylation was performed with higher catalyst loading (10 mol %) and temperature (−25 °C). Additionally, acetonitrile was employed as the solvent to influence the *β*-selectivity. On the other hand, when THF or a mixture of THF and $CH_3CN$ (1:4) was employed as the solvent in the glycosylation, disaccharide **6** was obtained as a 1:3 mixture of α- and *β*-isomers.

**TABLE 4.** ***β*-Selective Glycosylation with C(2)-PMB-Glucose Donor**[a]




| Entry | R'OH | Disaccharides | Yield[b] | β:α[c] |
|---|---|---|---|---|
| 1 | **7** |  **28** | 75% | 9:1 |
| 2 | **8** |  **29** | 90% | 8:1 |
| 3 | **10** |  **30** | 71% | 10:1 |
| 4 | **11** |  **31** | 71% | 6:1 |

[a] All reactions were performed in $CH_2Cl_2$ (0.15 M) with 2 mol % of $Pd(PhCN)_2Cl_2$ and 4 mol % of AgOTf. [b] Isolated yield. [c] $^1H$ NMR ratio.

The glycosyl trichloroacetimidates are generally activated with strong and moisture sensitive Lewis acids such as $BF_3 \cdot OEt_2$,[19] TMSOTf,[20] TBSOTf,[21] $Tf_2O$,[22] and $ZnBr_2$;[23] $BF_3 \cdot OEt_2$ has been among the widely used Lewis acids.[24] Glycosylation of galactosyl nucleophile **5** with trichloroacetimidate **4** was performed with 1 mol % of $BF_3 \cdot OEt_2$ at −78 °C so that we can determine the reactivity and selectivity of $BF_3 \cdot OEt_2$ compared to that of cationic Pd(II) species,

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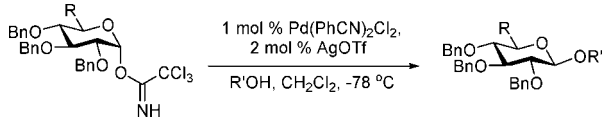
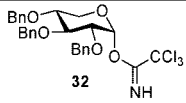
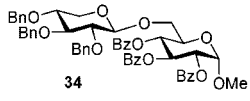
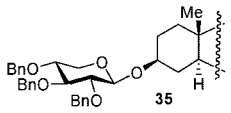
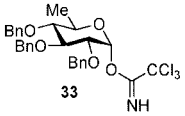
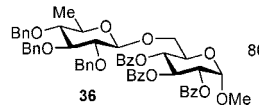
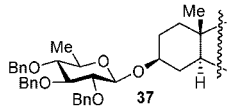
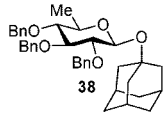
**TABLE 5. Selective Glycosylation with Benzylated Xylose and Quinovose Donors[a]**




| Entry | Donor | R'OH | Disaccharides | Yield[b] | β:α[c] |
|---|---|---|---|---|---|
| 1 |  **32** | 7 |  **34** | 85% | 11:1 |
| 2 | | 8 |  **35** | 76% | 10:1 |
| 3 |  **33** | 7 |  **36** | 80% | 7:1 |
| 4 | | 8 |  **37** | 86% | 5:1 |
| 5 | | 11 |  **38** | 88% | 8:1 |

[a] All reactions (except entries 2 and 4) were carried out in $CH_2Cl_2$ (0.15 M) with AgOTf and $Pd(PhCN)_2Cl_2$ at −78 °C. [b] Isolated yield. [c] $^1H$ NMR ratio.

$Pd(PhCN)_2(OTf)_2$ (Scheme 3). In this event, less than 5% conversion was observed even after the reaction had been stirred for 8 h.

The outcome of the Lewis acid experiment (Scheme 3) suggests that there is no turnover with use of $BF_3 \cdot OEt_2$ as a catalyst. In this glycosylation reaction, trichloroacetamide is generated as the byproduct (Scheme 4). Since $BF_3 \cdot OEt_2$ is quite oxophilic, it preferentially coordinates to the carbonyl oxygen of trichloroacetamide. Thus, this byproduct inhibition prohibits $BF_3 \cdot OEt_2$ from turnover. On the other hand, trichloroacetamide is not a good ligand for $Pd(PhCN)_2(OTf)_2$, thereby resulting in high turnover of the palladium catalyst.

To assess the scope of this new glycosylation method to direct the stereoselective formation of β-glycosidic linkages in the absence of the traditional C(2)-ester participatory group, a number of primary, secondary, and tertiary hydroxyls of carbohydrate acceptors (Scheme 5) were investigated with perbenzylated trichloroacetimidate donor **4**.

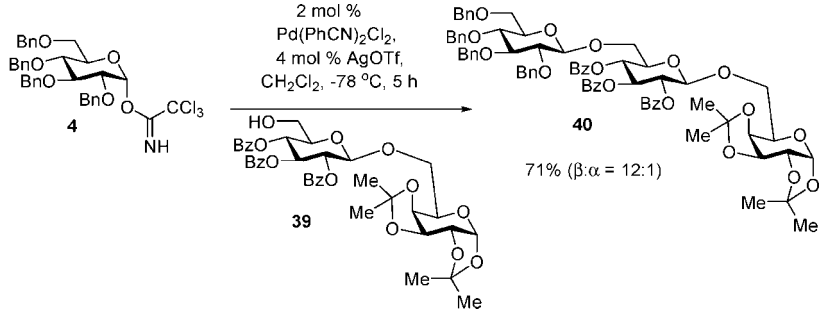
Under standard cationic palladium conditions, disaccharides **12**−**15** were isolated in good yields with excellent β-selectivity (Table 2). With use of dihydrocholesterol **8** as a glycosyl acceptor, the glycosylation reaction was performed at −45 °C as the reaction solidified at −78 °C (entry 2). We also tried to compare our cationic palladium results with other Lewis acid results.[1b] Apart from glycosyl acceptor **8**, most of these acceptors have not been investigated with perbenzylated trichloroacetimidate **4** under Lewis acid conditions. In the case of glycosyl nucleophile **8**, $Pd(PhCN)_2(OTf)_2$ provided disaccharide **19** with higher yield and selectivity than that of $BF_3 \cdot OEt_2$ (Table 2, entry 3).[15] In addition, the reaction required lower catalyst loading of $Pd(PhCN)_2(OTf)_2$ in comparison to $BF_3 \cdot OEt_2$. Furthermore, the higher temperature reaction (−40 to 25 °C) was required with use of $BF_3 \cdot OEt_2$ as an activating reagent.

Our next step was to determine how other ether protecting groups at the C(2)-position of glycosyl donors would affect the β-selectivity. Accordingly, the C(2)-allyl donors were examined with a variety of nucleophilic acceptors **7**−**11**. As shown in Table 3, the desired disaccharides **16**−**26** were also obtained in good yields with good to excellent β-selectivity. These results are encouraging because they suggest that cationic palladium catalyst selectively coordinates to the C(1)-imidate nitrogen in the presence of the allyl protecting group.

The results obtained in Tables 2 and 3 suggest that the C(2)-ether protecting groups (benzyl and allyl) in conjunction with the cationic palladium catalyst play important roles in controlling the β-selectivity at the newly formed glycosidic bonds. We also investigated the ability of the *p*-methoxybnezyl group to direct β-glycosylation since this protecting group has been extensively employed in glycosylation reaction with no or little effect on reactivity and selectivity in comparison to the benzyl group. The *p*-methoxybenzyl group can be orthogonally removed in the presence of the benzyl protecting group. Accordingly, selective coupling of 2,3,4,6-tetra-*O*-*p*-methoxybenzyl-D-glucopyranosyl trichloroacetimidate **27** with an array of nucleophilic acceptors provided the desired disaccharides **28**−**31** in good β-selectivity (Table 4). In these reactions, 2 mol % of the cationic palladium catalyst, $Pd(PhCN)_2(OTf)_2$, was required for the coupling to go to completion at −78 °C. Overall, the reaction of the *p*-methoxylbenzyl-protected donor **27** is less selective than that of the benzyl-protected donor **4**.

Encouraged by the results obtained with D-glucose donors, we decided to explore the feasibility of our cationic palladium method with tribenzylated D-xylose trichloroacetimidate donor **32** and D-quinovose trichloroacetimidate donor **33** (Table 5). These substrates are the carbohydrate moieties found within biologically important oligosaccharide natural

**SCHEME 6**



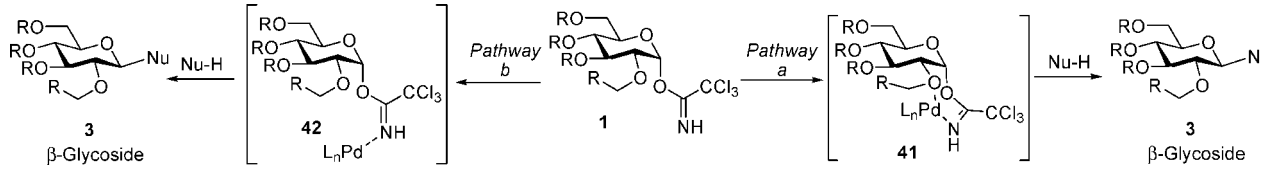
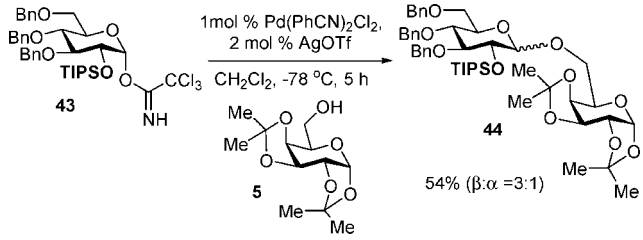
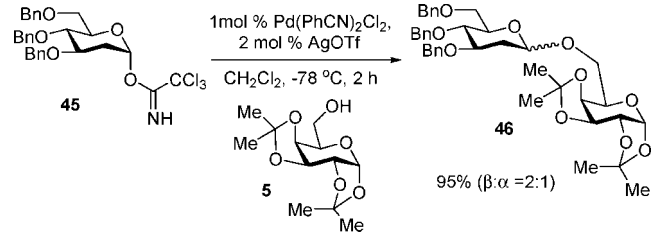



**FIGURE 1.** Proposed cationic Pd(II) directed β-stereoselective glycosylation.

**SCHEME 7**




**SCHEME 8**




products.[25] Since these substrates lack the protected C(6)-hydroxyl functionality, we are not sure how this would affect the β-selectivity. Gratifyingly, it was found that both trichloroacetimidates **32** and **33** were able to couple with a variety of primary and hindered alcohols to provide the desired disaccharides **34**−**38** in good yields with moderate to good β-selectivity (Table 5).

Many glycosylation methods work well to make disaccharides but potentially break down with oligosaccharides. Therefore, it is worth investigating the scope of the cationic palladium controlled β-glycosylation in the context of trisaccharide synthesis (Scheme 6). In a [1+2] approach, glycosylation of disaccharide nucleophile **39**[9] with trichloroacetimidate donor **4** under standard cationic palladium conditions provided the corresponding trisaccharide **40** in 71% yield with excellent β-selectivity (Scheme 6). This result illustrates the efficiency of this cationic palladium methodology, and it does so with the formation of **40** in excellent anomeric selectivity. In addition, the coupling was performed at −78 °C with only 2 mol % of $Pd(PhCN)_2(OTf)_2$ as the activating reagent.

A proposed mechanism for cationic palladium controlled β-glycosylation in the absence of the traditional C(2)-ester participatory group is outlined in Figure 1. It is hypothesized that the reaction might operate via a seven-membered-ring intermediate such as **41**, wherein the cationic Pd(II) species coordinates to both C(1)-imidate nitrogen and C(2)-oxygen of trichloroacetimidate donor **2** (pathway a). Formation of this seven-membered-ring intermediate directs the selectivity, leading to the formation of β-glycoside **3**. However, the possibility of the glycosylation reaction occurring through a simple $S_N2$ displacement without internal chelation cannot be ruled out (pathway b).

To differentiate between the two glycosylation reaction pathways, two control experiments were performed. In the first experiment, galactose acceptor **5** was coupled with C(2)-triisopropylsilyl protected donor **43** (Scheme 7). If the seven-membered-ring intermediate such as **41** (Figure 1) is the operative pathway, it is anticipated that disaccharide **44** will be formed as a mixture of α- and β-isomers because the bulky TIPS group prevents the palladium catalyst from coordinating to the C(2)-oxygen of glycosyl donor **43**. Accordingly, treatment of both coupling partners **5** and **43** under the standard cationic palladium(II) conditions provided the corresponding disaccharide **44** in 54% yield with β:α = 3:1 (Scheme 7). Thus, evidence suggests that the operative pathway is likely to be the seven-membered-ring intermediate (Figure 1, pathway a), in which the initial step of activation involves the coordination of Pd(II) species to both C(1)-imidate nitrogen and C(2)-oxygen of glycosyl donor.

A second experiment was carried out employing C(2)-deoxy glycosyl donor **45** (Scheme 8). Since there is no oxygen functionality at the C(2)-position of **46**, formation of a seven-membered-ring intermediate such as **41** (Figure 1, pathway a) cannot occur. Thus, if the seven-membered-ring pathway is operative, disaccharide **46** will be formed as a mixture of α- and β-isomers. On the other hand, if the simple $S_N2$ pathway without internal chelation is operative (Figure 1, pathway b), β-isomer of **46** will be formed as a major product. Accordingly, glycosylation of **5** with **45** provided disaccharide **46** as a mixture of α- and β-isomers (β:α = 2:1) (Scheme 8). The outcome of this experiment suggests that the $S_N2$ pathway without internal chelation is unlikely to be the major operative pathway under cationic palladium conditions.

The above experiments allow us to establish the possible mechanism of cationic palladium(II) catalyst directed β-selective glycosylation. The results obtained from C(2)-TIPS donor **43** (Scheme 7) and C(2)-deoxy donor **45** (Scheme 8) support that the seven-membered-ring pathway, wherein the palladium(II) species coordinates to both the C(1)-imidate nitrogen and C(2)-oxygen of glycosyl trichloroacetimidate donor, is likely to be the major operative pathway.

## Conclusions

In summary, a novel method for stereoselective synthesis of β-glycosides in the absence of the traditional C(2)-ester neighboring group participation has been developed. This approach relies on the nature of the cationic palladium(II) complex, $Pd(PhCN)_2(OTf)_2$, to control the β-selectivity. This new β-glycosylation method is applicable to a variety of glucose donors incorporating benzyl, allyl, and *p*-methoxybenzyl ether protecting groups at the C(2)-position as well as tribenzylated xylose and quinovose donors. The reaction is highly β-selective and proceeds under low temperature (−78 °C) with low catalyst

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loading (1−2 mol %). The efficiency of cationic palladium conditions has been applied to the synthesis of a number of disaccharides and trisaccharides with moderate to excellent $\beta$-selectivity. Mechanistic studies suggest that the reaction may operate via a seven-membered-ring pathway, in which the cationic Pd(II) species coordinates to both the C(1)-imidate nitrogen and C(2)-oxygen of glycosyl trichloroacetimidate donors. Formation of this seven-membered-ring intermediate directs the anomeric selectivity, leading to the formation of $\beta$-glycosides.

## 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 Disaccharide 6.** A 10 mL oven-dried Schlenk flask was charged with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate donor **4** (102 mg, 0.15 mmol, 1 equiv), 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **5** (51 mg, 0.195 mmol, 1.3 equiv), and $CH_2Cl_2$ (0.8 mL). The resulting solution was cooled to −78 °C, and a preformed solution of $Pd(PhCN)_2Cl_2$ (0.58 mg, 0.0015 mmol, 1 mol %) and AgOTf (0.77 mg, 0.003 mmol, 2 mol %) in $CH_2Cl_2$ (0.2 mL) was then added. The reaction mixture was stirred at −78 °C for 1 h, diluted with benzene (1 mL), and purified by silica gel flash chromatography (2/1, hexane/ethyl acetate) to give the desired disaccharide **6** (103 mg, 87%, $\beta$:$\alpha$ = 10:1) as a pale yellow oil. $R_f$ 0.36 (hexanes/ethyl acetate, 4/1); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.44−7.14 (m, 20H), 5.58 (d, $J$ = 5.0 Hz, 1H), 5.07 (d, $J$ = 11 Hz, 1H), 4.97 (d, $J$ = 11 Hz, 1H), 4.82 (d, $J$ = 11 Hz, 1H), 4.79 (d, $J$ = 11 Hz, 1H), 4.73 (d, $J$ = 11 Hz, 1H), 4.65−4.58 (m, 2H), 4.55 (s, 1H), 4.51 (d, $J$ = 11 Hz, 1H), 4.47 (d, $J$ = 7.5 Hz, 1H), 4.33−4.31 (m, 1H), 4.25 (d, $J$ = 8 Hz, 1H), 4.17 (dd, $J$ = 10.5, 3.5 Hz, 1H), 4.1 (m, 1H), 3.83−3.68 (m, 3H), 3.67−3.58 (m, 2H), 3.49−3.45 (m, 2H), 1.51 (s, 3H), 1.46 (s, 3H), 1.32 (2s, 6H);. $^1$H NMR matches with the literature report,[25] $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 138.7, 138.2, 128.7, 128.4, 128.2, 128.0, 127.9, 127.7, 127.6, 127.55, 127.49, 109.4, 108.6, 104.4, 96.4, 84.6, 81.6, 77.7, 75.7, 75.0, 74.8, 74.4, 73.5, 71.5, 70.8, 70.5, 69.7, 68.8, 67.4, 26.1, 26.0, 25.1, 24.5; $^{13}$C NMR matches with the literature report;[25] $J$($^{13}$CH) = 156 Hz (104.4 ppm), 179 Hz (96.4 ppm); IR (film, cm$^{-1}$) $\nu$ 2902, 1454, 1381, 1255, 1211.

**Preparation of Trisaccharide 40.** A 10 mL oven-dried Schlenk flask was charged with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate donor **4** (56 mg, 0.082 mmol, 1 equiv), disaccharide acceptor **39** (66 mg, 0.090 mmol, 1.1 equiv), and $CH_2Cl_2$ (0.6 mL). The resulting solution was cooled to −78 °C, and a preformed solution of $Pd(PhCN)_2Cl_2$ (0.62 mg, 0.0016 mmol, 2 mol %) and AgOTf (0.84 mg, 0.0032 mmol, 4 mol %) in $CH_2Cl_2$ (0.2 mL) was then added. The reaction mixture was stirred at −78 °C for 5 h, diluted with benzene (1 mL), and purified by silica gel flash chromatography (2/1, hexane/ethyl acetate) to give the desired disaccharide **40** (73 mg, 71%, $\beta$:$\alpha$ = 12:1) as a pale yellow oil. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.94 (d, $J$ = 7.0 Hz, 2H), 7.90 (d, $J$ = 7.0 Hz, 2H), 7.79 (d, $J$ = 8.0 Hz, 2H), 7.48−7.12 (m, 29H), 5.85 (t, $J$ = 9.5 Hz, 1H), 5.48 (t, $J$ = 8.5 Hz, 1H), 5.41 (t, $J$ = 9.5 Hz, 1H), 5.36 (d, $J$ = 4.5 Hz, 1H), 4.98 (d, $J$ = 11.0 Hz, 1H), 4.91 (d, $J$ = 8.5 Hz, 1H), 4.88 (d, $J$ = 8.5 Hz, 1H), 4.77 (d, $J$ = 11.0 Hz, 1H), 4.73 (d, $J$ = 10.5 Hz, 1H), 4.68 (d, $J$ = 11.0 Hz, 1H), 4.53 (d, $J$ = 12.5 Hz, 1H), 4.47 (d, $J$ = 7.0 Hz, 1H), 4.41 (d, $J$ = 12.0 Hz, 1H), 4.37 (d, $J$ = 8.0 Hz, 1H), 4.16−4.04 (m, 3H), 3.97−3.91 (m, 2H), 3.87−3.72 (m, 4H), 3.62−3.51 (m, 5H), 3.39 (t, $J$ = 7.5 Hz, 2 H), 1.30 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 165.7, 165.4, 165.2, 138.6, 138.5, 138.1, 133.4, 133.3, 133.1, 133.0, 130.1, 129.8, 129.7, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.69, 127.6, 127.5, 109.1, 108.3, 103.8, 101.3, 96.1, 84.6, 82.0, 77.6, 75.7, 74.9, 74.8, 74.7, 74.0, 73.4, 73.1, 71.8, 70.8, 70.5, 70.4, 70.2, 68.7, 68.6, 68.5, 67.3, 25.8, 25.6, 24.8, 24.1; IR (film, cm$^{-1}$) $\nu$ 3063, 3030, 2986, 2922, 1733, 1452, 1281, 1260, 1093, 1069, 1027, 709; $J$($^{13}$CH) = 166 Hz (94.4 ppm); HRMS (ESI) calcd for $C_{73}H_{76}O_{19}Na$ (M + Na) 1279.48730, found 1279.47682.

**Preparation of Disaccharide 44.** A 10 mL oven-dried Schlenk flask was charged with 3,4,6-tribenzyl-2-triisopropylsilyl-*O*-D-glucopyranosyl trichloroacetimidate **43** (60 mg, 0.080 mmol, 1 equiv), 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **5** (27 mg, 0.10 mmol, 1.3 equiv), and $CH_2Cl_2$ (0.6 mL). The resulting solution was cooled to −78 °C, and a preformed solution of $Pd(PhCN)_2Cl_2$ (0.31 mg, 0.0006 mmol, 1 mol %) and AgOTf (0.41 mg, 0.0016 mmol, 2 mol %) in $CH_2Cl_2$ (0.2 mL) was then added. The reaction mixture was stirred at −78 °C for 5 h, diluted with benzene (1 mL), and purified by silica gel flash chromatography (6/1, hexane/ethyl acetate) to give the desired disaccharide **44** (37 mg, 54%, $\beta$:$\alpha$ = 3:1) as a pale yellow oil. $R_f$ 0.36 (hexanes/ethyl acetate, 6/1); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.34−7.26 (m, 9H), 7.22−7.20 (m, 4H), 7.07 (t, $J$ = 3.5 Hz, 1H), 7.02−7.01 (m, 1H), 5.49 (d, $J$ = 5 Hz, 1H), 5.48 (d, $J$ = 5 Hz, 0.3H), 4.93 (d, $J$ = 11.5 Hz, 1H), 4.87 (d, $J$ = 11 Hz, 1H), 4.83−4.80 (m, 1H), 4.74−4.69 (m, 1H), 4.65−4.62 (m, 1H), 4.59−4.58 (m, 1H), 4.55−4.52 (m, 1H), 4.49−4.45 (m, 1H), 4.42 (d, $J$ = 10.5 Hz, 1H), 4.29−4.25 (m, 2H), 4.11 (dd, $J$ = 10, 5 Hz, 0.3H), 3.99 (t, $J$ = 7 Hz, 1H), 3.89 (d, $J$ = 3 Hz, 0.3H), 3.88 (d, $J$ = 3.5 Hz, 1H), 3.85 (d, $J$ = 8.5 Hz, 1H), 3.83−3.80 (m, 1H), 3.77−3.74 (m, 2H), 3.71−3.69 (m, 1H), 3.67−3.60 (m, 3H), 3.56 (dd, $J$ = 11, 7.5 Hz, 0.3H), 3.51 (t, $J$ = 8.5 Hz, 0.3H), 3.44 (d, $J$ = 10.5 Hz, 0.3H), 1.51 (d, $J$ = 16.5 Hz, 3H), 1.40 (s, 3H), 1.32−1.29 (m, 6H), 1.21−1.16 (m, 1H), 1.06−1.03 (m, 20H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 139.3, 139.0, 138.4, 138.2, 138.0, 128.3, 128.2, 128.1, 128.08, 128.03, 127.95, 127.83, 127.8, 127.64, 127.6, 127.5, 127.2, 127.1, 109.2, 109.1, 108.6, 108.4, 103.7, 99.8, 96.32, 96.25, 86.6, 82.8, 78.2, 78.0, 75.6, 75.4, 75.2, 74.9, 74.8, 74.7, 73.9, 73.6, 73.5, 71.5, 70.9, 70.7, 70.5, 70.47, 70.2, 68.8, 68.5, 67.1, 66.74, 66.66, 26.1, 26.0, 25.99, 24.98, 24.6, 24.4, 18.2, 18.11, 18.06, 13.1, 12.7; IR (film, cm$^{-1}$) $\nu$ 2939, 2868, 1498, 1457, 1377, 1252, 1214, 1160, 1005, 917, 883, 735, 692; HRMS (ESI) calcd for $C_{48}H_{68}O_{11}Si$ Na (M + Na) 871.44231, found 871.44197.

**Preparation of Disaccharide 46.** A 10 mL oven-dried Schlenk flask was charged with 2-deoxy-3,4,6-tri- benzyl-*O*-D-glucopyranosyl trichloroacetimidate **45** (75 mg, 0.129 mmol, 1 equiv), 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **5** (44 mg, 0.168 mmol, 1.3 equiv), and $CH_2Cl_2$ (1 mL). The resulting solution was cooled to −78 °C, and a preformed solution of $Pd(PhCN)_2Cl_2$ (0.50 mg, 0.00129 mmol, 1 mol %) and AgOTf (0.66 mg, 0.00258 mmol, 2 mol %) in $CH_2Cl_2$ (0.2 mL) was then added. The reaction mixture was stirred at −78 °C for 2 h, diluted with benzene (1 mL), and purified by silica gel flash chromatography (4/1, hexane/ethyl acetate) to give the desired disaccharide **46** (83 mg, 95%, $\beta$:$\alpha$ = 3:1) as a pale yellow oil. $R_f$ 0.32 (hexanes/ethyl acetate, 4/1); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.32−7.27 (m, 14), 7.18 (d, $J$ = 4.5 Hz), 5.54 (d, $J$ = 21 Hz, 1H), 5.53 (d, $J$ = 19.5, 0.3H), 5.03 (s, 0.3H), 4.90−4.87 (m, 2H), 4.69−4.58 (m, 6H), 4.54−4.50 (m, 5H), 4.31 (s, 2H), 4.21 (d, $J$ = 6.5 Hz, 2H), 4.09 (d, $J$ = 11.5 Hz, 1H), 4.00−3.94 (m, 2H), 3.79 (t, $J$ = 9 Hz, 1H), 3.72−3.65 (m, 6H), 3.54 (t, $J$ = 9 Hz, 1H), 3.39 (d, $J$ = 8 Hz, 1H), 2.48 (d, $J$ = 11 Hz, 1H), 2.33 (d, $J$ = 13 Hz, 0.3H), 1.74 (d, $J$ = 12.5 Hz, 0.3H), 1.65 (dd, $J$ = 23, 12 Hz, 1H), 1.53 (s, 3H), 1.51 (s, 1H), 1.43 (s, 5H), 1.32 (s, 9H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 138.7, 138.5, 138.4, 138.3, 138.2, 138.1, 138, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 109.4, 109.3, 108.7, 108.6, 100.5, 97.3, 96.3, 79.3, 78.2, 77.9, 77.5, 75.0, 74.9, 71.8, 71.5, 71.2, 71.0, 70.9, 70.7, 70.6, 70.4, 69.1, 68.9, 68.7, 67.7, 65.7, 65.4, 36.5, 35.4, 26.2, 26.1, 26.0, 25.0, 24.9, 24.6, 24.4; IR (film, cm$^{-1}$) $\nu$ 3061,

3031, 2988, 2939, 2900, 2863, 1603, 1496, 1454, 1381, 1255, 1209, 1068; HRMS (ESI) calcd for $C_{39}H_{48}O_{10}Na$ (M + Na) 699.31397, found 699.31658.

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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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