Communication

Modular and Stereoselective Synthesis of C-Aryl Glycosides via Catellani Reaction

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Modular and Stereoselective Synthesis of C-Aryl Glycosides via Catellani Reaction

Weiwei Lv, Yanhui Chen, Si Wen, Dan Ba, and Guolin Cheng*

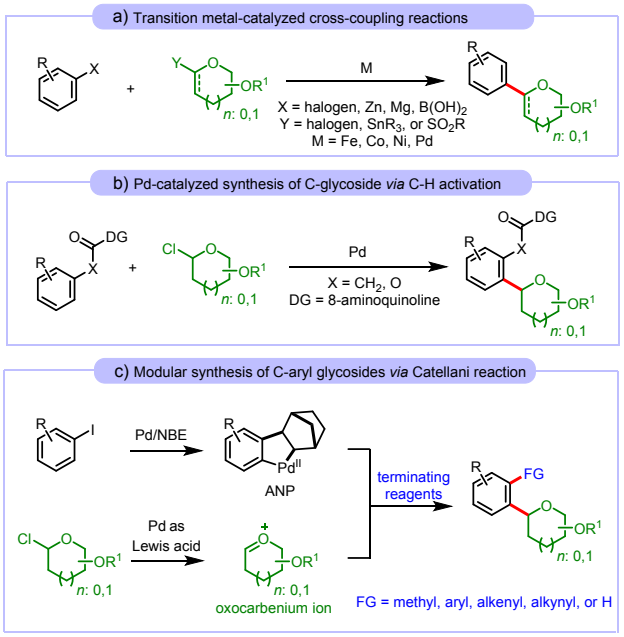
College of Materials Science & Engineering, Huaqiao University, Xiamen 361021, China

ABSTRACT: In this work, we describe a Catellani-type C−H glycosylation to provide rapid access to various highly decorated α-C-(hetero)aryl glycosides in a modular and stereoselective manner (>90 examples). The termination step is flexible, which is demonstrated by *ipso*-Heck reaction, hydrogenation, Suzuki coupling, and Sonogashira coupling. Application of this methodology has been showcased by preparing glycoside–pharmacophore conjugates and a dapagliflozin analogue. Notably, the technology developed herein represents an unprecedented example of Catellani-type alkylation involving a S_N1 pathway.

C-Glycosides have been widely used as carbohydrate mimetics due to their high chemical and metabolic stability compared with the O-linked glycosides.[1,2] A privileged class of C-glycosides containing an aryl aglycone is known as C-aryl glycosides, which are essential structural moieties in many natural products[3] and drug candidates.[4] Traditional methods to synthesize those compounds include Friedel–Crafts-type arylation of glycosyl phosphates with electron-rich arenes[5] and nucleophilic substitutions of metallated arenes to glycosyl precursors.[6] These methods often have narrow substrate scope, poor functional group compatibility, and low stereoselectivity. In the past decade, transition metal-catalyzed cross-coupling reactions between both pre-functionalized glycosyl precursors and aryl partners have been achieved for the preparation of a range of C-aryl glycosides (Scheme 1a).[7−12] These successful examples reveal the possibility of direct glycosylation of arenes *via* transition metal-catalyzed C−H activation.[13] Recently, Chen reported the first Pd-catalyzed 8-aminoquinoline directed *ortho*-C−H glycosylation, in which the *in situ* generated oxocarbenium ion intermediates were involved (Scheme 1b).[14a] Despite this elegant directed C−H glycosylation, the development of other non-directed C−H glycosylations, especially in a modular and stereoselective manner, is still highly desirable.

As a part of our ongoing interest in Catellani-type C−H functionalizations,[15] we questioned whether a modular and stereoselective processes aimed at making C-aryl glycosides could be achieved *via* Catellani reaction.[16,17] To realize this goal, two main challenges should be taken into consideration: 1) the Low reactivity of secondary alkyl halides in Catellani reaction,[18] and 2) the control of anomeric configuration of the C-glycoside products. Since the first *ortho*-alkylation of aryl iodides was reported by Catellani in 1997,[19] a range of functionalized alkyl halides,[16d] epoxides,[20] and aziridines[21] were successfully employed as alkylating reagents in Catellani reaction. However, those alkylating reagents are generally limited to less sterically hindered primary alkyl halides and terminal strained rings. The applications of secondary alkyl halides are rare due to the sluggish oxidative addition of Pd to alkyl−X bonds and the facile β-hydride elimination of resultant alkyl Pd species. Only one example involving secondary alkyl iodides in Catellani reaction was reported by Lautens and the complete inversion of stereochemical information using chiral starting materials supported a S_N2 mechanism.[22] We speculated that oxocarbenium ion may be generated from glycosyl halide using Pd as Lewis acid, such highly reactive intermediate may react with arylnorbornylpalladacycle (ANP) through a S_N1 pathway,[23] thus generating *ortho*-glycosyl aryl Pd species that is a versatile intermediate in a variety of cross-coupling reactions (Scheme 1c). We also proposed that the steric interactions between oxocarbenium ion and ANP may play a key role in dictating the stereoselectivity. Herein we disclosed the first Catellani-type C−H glycosylation of (hetero)aryl iodides to generate a wide range of α-C-aryl glycosides.

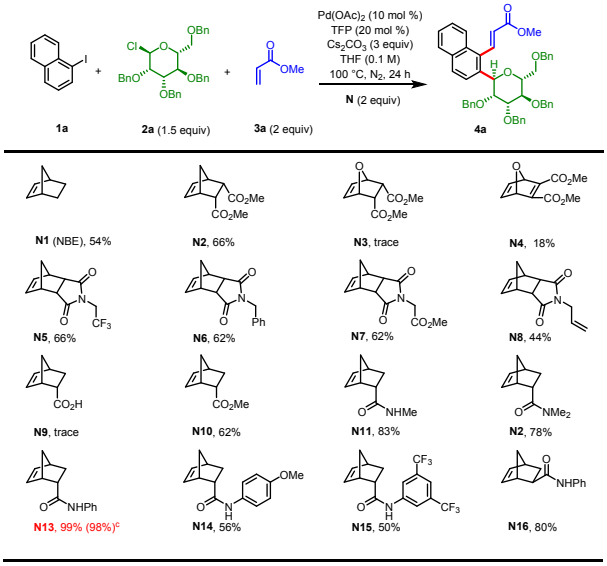
Scheme 1. Synthetic Methods for the Construction of C-Aryl Glycosides.



We began our work by studying the reaction of 1-iodonaphthalene (**1a**), tetrabenzyl-protected α-mannosyl

chloride (**2a**), and methyl acrylate (**3a**) using Pd/norbornene (NBE) cooperative catalysis. After intensive investigation, we found that the desired α-C-aryl mannoside (**4a**) could be obtained in 54% yield under similar reaction conditions reported by Lautens,[17p] namely, $Pd(OAc)_2$ (10 mol%), tri(2-furyl)phosphane (TFP, 20 mol %), NBE (**N1**, 2 equiv), Cs_2CO_3 (3 equiv) in THF under N_2 at 100 °C (see Table S1–S3 of Supporting Information for details). We then systematically evaluated the influence of a wide spectrum of NBEs on the reactivity of this transformation (Table 1). It is noteworthy that NBE is crucial for this reaction as no product (**4a**) was observed in the absence of the NBE. While 2,3-dicarbomethoxy-7-oxa norbornene (**N3**) and 2,3-dicarbomethoxy-7-oxanorbornadiene (**N4**) dramatically decreased the yields of **4a**, and succinimide-containing NBEs (**N5-N8**) gave the desired product in 44-66% yields. Further investigations showed that the amide-substituted NBE (**N11**),[17l] was found to give a 83% yield of **4a**. Delightfully, NBE bearing an anilide moiety (**N13**) could give the optimal result. It should be noted that exclusive α-isomer was observed in all cases of the above mentioned reactions.

Table 1. NBEs Evaluation for Catellani-type C−H Glycosylation[a,b]

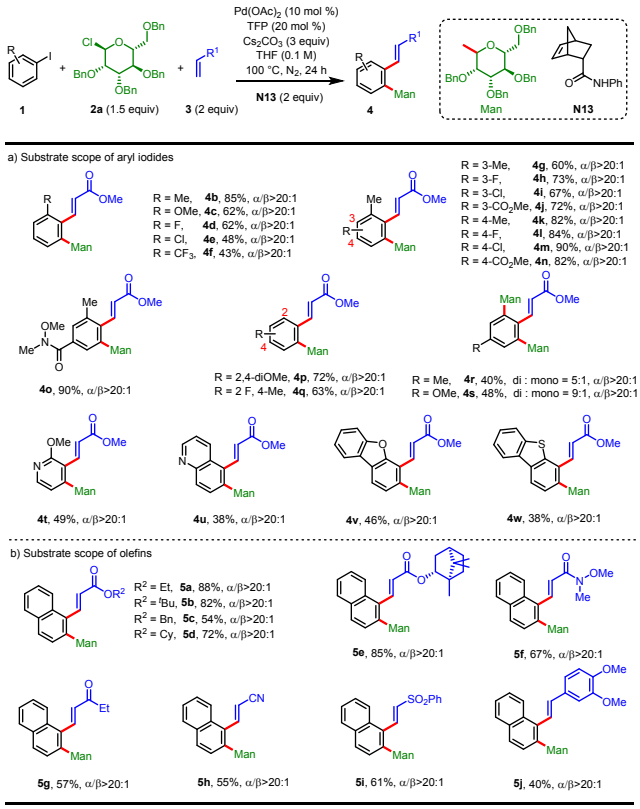


[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), **3a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), TFP (20 mol %), NBE (2 equiv), and Cs_2CO_3 (3 equiv) in THF (1 mL) under N_2 at 100 °C. [b]Yields were determined by ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard. [c]Isolated yield.

With optimized reaction conditions in hand, it was found that the reaction process can be extended to a large variety of substituted iodobenzenes, thus giving the desired α-C-aryl mannoside products (**4a**–**q**) in 43-98% yields (Table 2a). Various valuable functional groups, including methoxyl, fluoro, chloro, trifluoromethyl, ester, and Weinreb amide, were compatible with the reaction conditions. It is noteworthy that dimannosylation products were observed as major products when *para*-substituted iodobenzenes (**4r** and **4s**) were subjected to the reaction. Notably, the coordinative pyridyl and quinolyl iodides gave the desired products (**4t** and **4u**) in 48% and 38% yields, respectively. Dibenzo[*b*,*d*]furan and dibenzo[*b*,*d*]thiophene-containing products (**4v** and **4w**) could also be formed without obstacle.

Next, we evaluated the scope of olefin terminating reagents as depicted in Table 2b. Various α,β-unsaturated olefins could serve as particularly effective terminating reagents for this Catellani-type C−H mannosylation (**5a**–**i**); for example, the reactions with ethyl, *tert*-butyl, cyclohexyl, and isobornyl acrylates proceeded in 54%–88% yields (**5a**–**e**). Likewise, other activated olefins bearing electron-withdrawing groups, including Weinreb amide, ketone, nitrile, and sulfone, were also employed to provide the corresponding products in good yields (**5f**–**i**). We also noted that 3,4-dimethoxy-styrene was compatible with this transformation, giving product (**5j**) in 40% yield.

Table 2. Substrate Scope of Aryl Iodides and Olefins for Catellani-type C−H Glycosylation Terminated by Heck Reaction.[a]

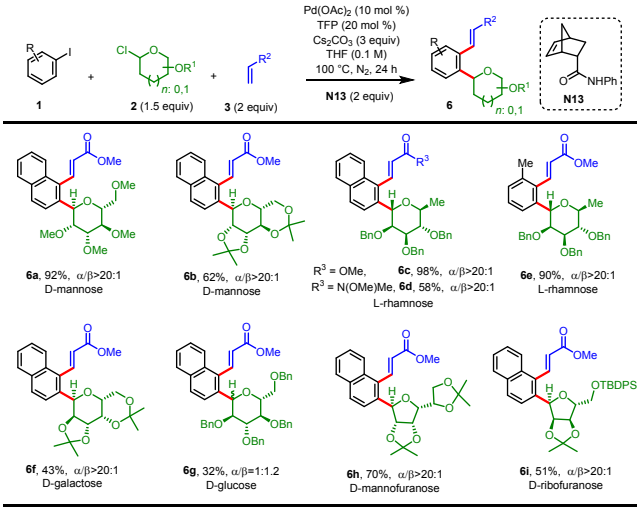


[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), **3** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), TFP (20 mol %), **N13** (2 equiv), and Cs_2CO_3 (3 equiv) in THF (1 mL) under N_2 at 100 °C.

Inspired by these exciting results, the scope of other glycosyl chlorides was explored (Table 3). Tetramethyl-protected α-mannosyl chloride smoothly underwent the reaction to deliver the corresponding product (**6a**) in 92% yield. 2,3,4,6-Di-*O*-isopropylidene-α-mannosyl chloride yielded the corresponding α-C-aryl mannoside (**6b**) in 62% yields. Delightfully, α-rhamnosyl chloride deriving from L-rhamnose was a suitable substrate to provide α-C-aryl rhamnosides (**6c**–**e**) in good to excellent yields. In addition, α-C-aryl galactoside (**6f**) was synthesized from α-galactosyl chloride. However, the reaction of α-glucosyl chloride with 1-iodonaphthalene (**1a**), and methyl acrylate (**3a**) afforded the desired C-aryl glucoside (**6g**) in 32% yield (α/β = 1:1.2). Notably, α-C-aryl mannofuranoside (**6h**) was afforded from the corresponding α-furanosyl chloride. Lastly, α-

ribofuranosyl chloride also delivered the product (**6i**) in average yield.

Table 3. Substrate Scope of Glycosyl Chlorides for Catellani-Type C−H Glycosylation.[a]



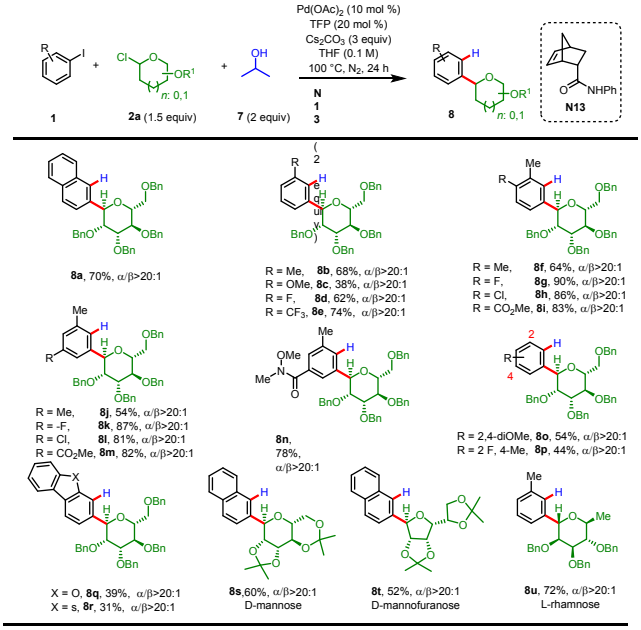
[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **3** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), TFP (20 mol %), **N13** (2 equiv), and Cs_2CO_3 (3 equiv) in THF (1 mL) under N_2 at 100 °C.

To further demonstrate the synthetic value of this Catellani-type C−H glycosylation, we then explored other *ipso*-termination processes (Table 4–6). To our delight, the reactions of aryl iodides (**1**), α-mannosyl chlorides **(2a** and **2c)**, and isopropanol (**7**) proceeded smoothly without modifying the standard conditions to deliver the desired α-C-aryl mannosides (**8a**–**s**) in 31–90% yields (Table 4).[24] Moreover, α-C-aryl rhamnosides (**8t**) and α-C-aryl mannofuranoside (**8u**) were obtained in 72% and 52% yields, respectively.

We further evaluated the Suzuki–Miyaura termination (Table 5). The "magic methyl" group can modulate the biological activity of pharmaceutical molecules, thus plays a vital role in drug discovery.[25] Delightfully, the methyl group was introduced for the first time onto the *ipso*-position of aryl iodides under Catellani reaction conditions using methylboronic acid as coupling partner. A rang of *ipso*-methylation products (**10a**–**f**) were synthesized in moderate yields. However, *ipso*-hydrogenation product (**8a**) rather than *ipso*-ethylation product was isolated in 42% yield when ethylboronic acid was used as terminating reagents. In this case, alkylboronic acid may serve as a reductant. Importantly, *ipso*-arylation products (**10g**–**k**) could be generated in 32%–56% yields under minor modification conditions (see Table S4 of Supporting Information for more information).

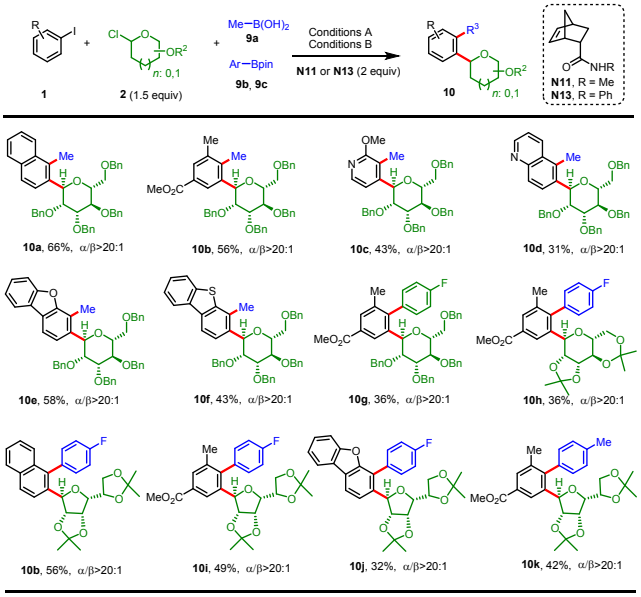
As to *ipso*-Sonogashira coupling termination,[26] a slight modification of the reaction conditions is required, including the employment of **N11** as a mediator, K_2CO_3 as the base, and a solvent change to CH_3CN (see Table S5 of Supporting Information for more information). We found that (triisopropylsilyl) acetylene **11a** could incorporated into the final products (**12a**–**j**), albeit in low yields, with the direct Sonogashira coupling byproducts mainly contributing to the mass balance (Table 6). More importantly, propargyl silyl ether **11b** was successfully applied to Catellani reaction for the first time to give the corresponding product (**12k**) in 35% yield. We noticed that the acetylene motif could serve as a linchpin to introduce carbonyl-containing pharmacophores onto glycosides. Thus, carbonyl-containing pharmacophores could be conjugated to C-glycosides *via* this Catellani-type C−H glycosylation, which was demonstrated by the preparation of mannoside-estradiol conjugate (**12l**) and mannofuranoside-estradiol conjugate (**12m**).

Table 4. Substrate Scope of Aryl Iodides and Glycosyl Chlorides for Catellani-Type C−H Glycosylation Terminated by Hydrogenation.[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), **7** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), TFP (20 mol %), **N13** (2 equiv), and Cs_2CO_3 (3 equiv) in THF (1 mL) under N_2 at 100 °C.

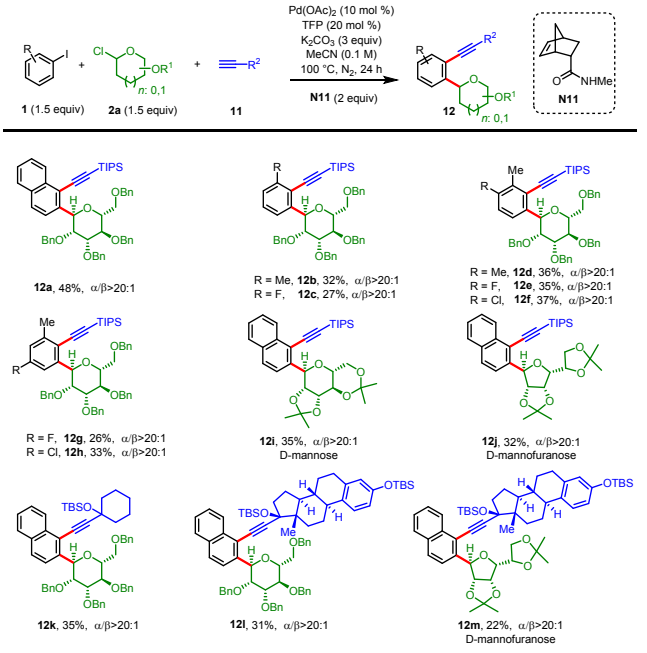
Table 5. Substrate Scope of Aryl Iodides and Boronic Acids for Catellani-Type C−H Glycosylation Terminated by Suzuki Coupling.[a]



[a]Reaction conditions A: **1** (0.1 mmol), **2a** (0.15 mmol), **9a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), TFP (20 mol %), **N13** (2 equiv), and Cs_2CO_3 (3 equiv) in THF (1 mL) under N_2 at 100 °C. Reaction conditions B: **1** (0.1 mmol), **2** (0.15 mmol), **9b** or **9c** (0.2

mmol), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol %), **N11** (2 equiv), and Cs_2CO_3 (3 equiv) in toluene (1 mL) under N_2 at 100 °C.

Table 6. Substrate Scope of Aryl Iodides and Alkynes for Catellani-Type C−H Glycosylation Terminated by Sonogashira Coupling.[a]

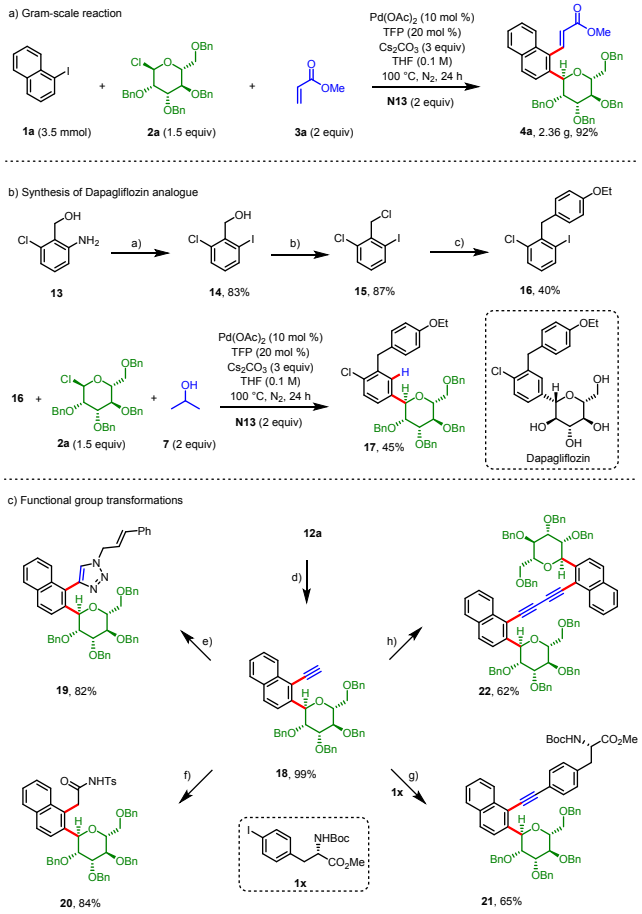


[a]Reaction conditions: **1** (0.15 mmol), **2a** (0.15 mmol), **8** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), TFP (20 mol %), **N11** (2 equiv), and K_2CO_3 (3 equiv) in CH_3CN (1 mL) under N_2 at 100 °C.

To prove the applicability of this transformation, a gram-scale reaction of **1a** with **2a** and **3a** was conducted to afford **4a** in comparable yield (92%) to that of the original value (Scheme 2a). Then, we applied our method to the preparation of a dapagliflozin analogue (Scheme 2b). Substituted aniline (**13**) could convert to aryl iodide (**16**) in 29% total yield, which further reacted with α-mannosyl chloride (**2a**) and isopropanol (**7**) to give the analogue of the dapagliflozin (**17**) in 45% yield. It is worth mentioning that aryl acetylene (**18**), which was obtained by desilylation of **12a**, is versatile synthetic intermediate (Scheme 2c). For example, mannoside-triazole conjugate (**19**) was synthesized in 82% yield from **18** *via* "click" reaction. In addition, **18** reacted with TsN_3 and H_2O to give amide (**20**) in high yield in the presence of a copper catalyst. Furthermore, the Sonogashira coupling of **18** with aryl iodide (**1x**) generated the mannoside-phenylalanine conjugate (**21**) in good yield. Gratifyingly, 1,3-diyne product (**22**) was obtained *via* copper-catalyzed homocoupling of **18** in 62% yield.

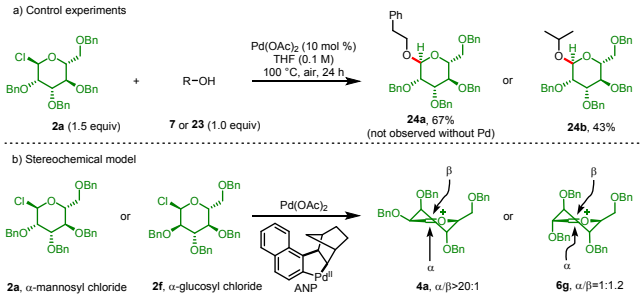
It should be noted that a catalytic amount of $Pd(OAc)_2$ could promote the formation of oxocarbenium ion intermediate efficiently, which was captured by primary and secondary alcohols to give **24a** and **24b** in good yields (Scheme 3a). The stereochemistry of this reaction could be elucidated by the stereochemical model between ANP and the oxocarbenium ions. As shown in Scheme 3b, oxocarbenium ion generated from α-mannosyl chloride is preferentially attacked from the α-face. Whereas α-glucosyl chloride-based oxocarbenium ion could be attacked from both α- and β-face, leading to **6g** in low yield with poor diastereoselectivity due to steric hindrance. These results indicated that a S_N1 pathway may be involved in this reaction.

Scheme 2. Gram-Scale Reaction, Synthetic Application, and Functional Group Transformations.



Reaction conditions: a) **13** (3 mmol), HCl (con., 0.68 mL), $NaNO_2$ (4 mmol) and H_2O in acetone (10 ml) at 0 °C. b) **14** (2.1 mmol), Et_3N (6.3 mmol), and $MeSO_3Cl$ (6.3 mmol) in CH_2Cl_2 (20 ml). c) 4-Ethoxyphenylboronic acid (0.5 mmol), KF (5 mmol) and **15** (0.5 mmol) in DCE (3.0 ml) at 100 °C. d) **9a** (1 mmol), TBAF (1 M in THF, 1.2 equiv) in THF (5 mL) at room temperature; e) **11** (0.1 mmol), (*E*)-(3-azidoprop-1-en-1-yl)benzene (1.5 equiv), CuI (5 mol %), DIPEA (10 mol %), and HOAc (10 mol %) in DCM (1 mL) at 70 °C under nitrogen atmosphere; f) **11** (0.1 mmol), TsN_3 (1.2 equiv), CuI (10 mol %), and Et_3N (0.12 mmol) in ^{t}BuOH/H_2O (2:1, 1 mL) at 70 °C under nitrogen atmosphere; g) **11** (0.1 mmol), **1t** (0.11 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), and Et_3N (1.5 equiv) in THF (1 mL) at 70 °C; h) **11** (0.1 mmol), CuI (2 mol %), and $BnNH_2$ (10 mol %) in THF (1 mL) at room temperature under oxygen atmosphere.

Scheme 3. Control Experiments and Stereochemical model.



In summary, we described the first example of modular synthesis of C-aryl glycosides *via* Catellani-type C−H glycosylation. This procedure features broad substrate scope and exceptionally high stereoselectivity. Exclusive α isomers were detected in all results with only one exception of C-aryl glucoside, which was obtained as a mixture of 1:1.2 anomers. The stereochemistry observed in the C−H glycosylation step strongly supports a S_N1 pathway, which may involve oxocarbenium ion intermediates. This technology enables the straightforward access to various highly decorated C-(hetero)aryl glycosides and glycoside–pharmacophore conjugates, which will create new opportunities to the development of glycoside–conjugate based therapeutics.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of new compounds, and X-ray data for **4n** (CCDC 1996105)

AUTHOR INFORMATION

Corresponding Author

*E-mail: glcheng@hqu.edu.cn

Notes

The authors declare no competing financial interest.

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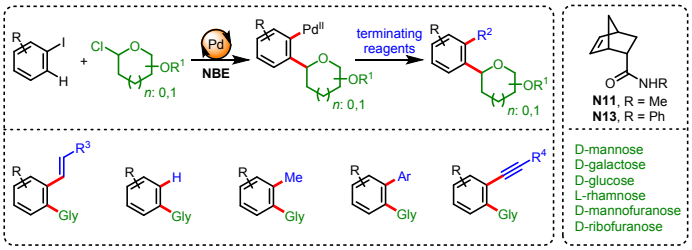
terminating reagents
NBE
n: 0,1
N11, R = Me
N13, R = Ph
D-mannose
D-galactose
D-glucose
L-rhamnose
D-mannofuranose
D-ribofuranose