Organic LETTERS

Letter

pubs.acs.org/OrgLett

Ligand-Controlled Monoselective *C*-Aryl Glycoside Synthesis via Palladium-Catalyzed C−H Functionalization of *N*-Quinolyl Benzamides with 1-Iodoglycals

Minglong Liu,[†] Youhong Niu,[†] Yan-Fen Wu,* and Xin-Shan Ye*

State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road No. 38, Beijing 100191, China

Supporting Information

ABSTRACT: A monoselective synthesis of aryl-*C*-$\Delta^{1,2}$-glycosides from 1-iodoglycals via palladium-catalyzed *ortho*-C−H activation of *N*-quinolyl benzamides has been developed. An amino acid derivative was used as a crucial ligand to improve the yield and monoselectivity of the coupling reaction. The utility of this protocol was demonstrated by a concise synthesis of key moieties of some natural products.

C-Glycosides are important carbohydrate congeners of *O*-glycosides that are stable to hydrolytic or enzymatic cleavage. *C*-Aryl glycosides belong to a subclass of *C*-glycosides. This subclass of sugar derivatives contains vital motifs of a number of biologically active natural products and medicinally valuable compounds with antidiabetic, antibacterial, and antitumor activities (Figure 1).[1] *C*-Aryl glycals are particularly

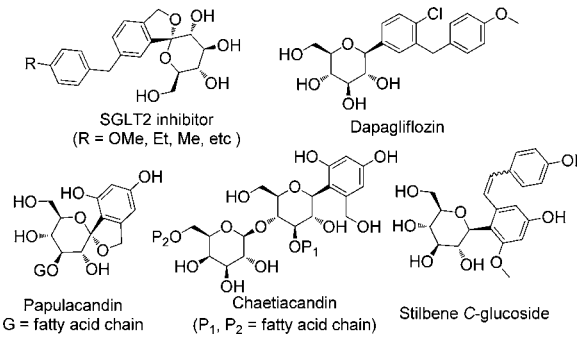
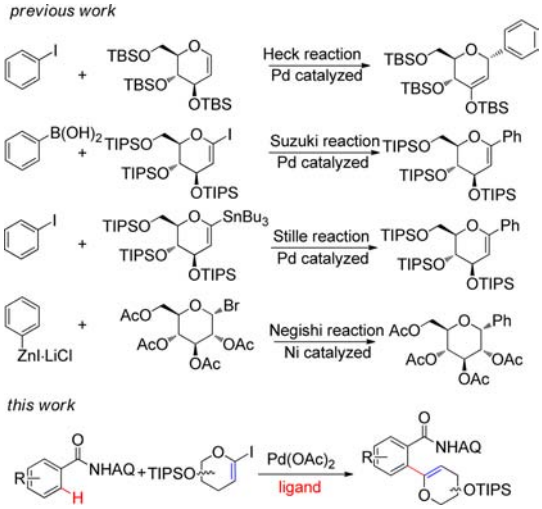


Figure 1. Some bioactive natural products and drugs.

useful synthons for the construction of different sugar moieties because the 1,2-double bond can be further transformed into various functionalities.

Various cross-coupling reactions are employed for the synthesis of *C*-aryl glycals and glycosides. General methods include the use of coupling of glycals with aryl halides,[2] coupling of C1-stannylated or boronated glycals with aryl halides,[3] coupling of glycals with boronic acids or carboxylic acids,[4] coupling reactions between glycal derivatives and organometallic reagents,[5] and Negishi coupling reactions between glycosyl halides and organozinc reagents (Scheme 1).[6] In most cases, both reactants have to be preactivated, and one of them has to be an organometallic reagent. Therefore, the development of more straightforward, atom-economic, and environmentally benign

Scheme 1. Synthesis of Glycals and *C*-Glycosides



methods for the synthesis of *C*-aryl glycosides is still of great significance.

Transition-metal-catalyzed, directing-group-mediated C−H functionalization has emerged as a powerful method for the construction of organic molecules in the last two decades.[7] Among these transformations, Pd-catalyzed C(sp^2)−H activation, in combination with its subsequent cross-coupling reaction with simple alkynes, alkenes, allenes, arenes, and heteroatoms,[7e,8] has generated many aromatic compounds with different scaffolds. In particular, C−H activation of aromatic acids and their derivatives followed by modification with aryl iodides[9] or alkenyl iodides[10] provides a reliable approach to synthesizing biphenyl or vinylbenzene derivatives. Given these reports, we

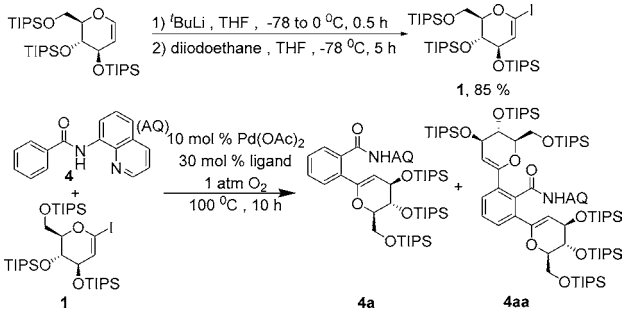
Received: February 29, 2016
Published: March 30, 2016

DOI: 10.1021/acs.orglett.6b00566
Org. Lett. 2016, 18, 1836−1839

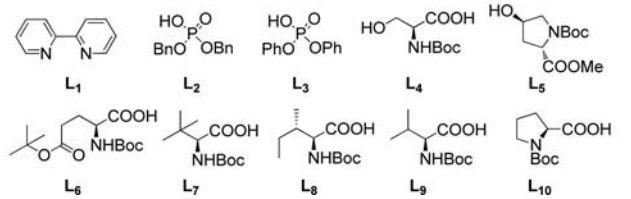
envisioned that a direct C−H functionalization of benzoic acid derivatives might be possible with 1-iodoglycals, though 1-iodoglycals are much more complicated substrates than simple aryl and alkenyl iodides. Herein, we report the synthesis of aryl-*C*-$\Delta^{1,2}$-glycosides by Pd-catalyzed, *N*-quinolyl-group-directed *ortho*-C−H functionalization of benzoic acid derivatives with 1-iodoglycals.[11]

Initially, the reaction of *N*-quinolyl benzamide (**4**)[12] and triisopropylsilyl-protected 1-iodoglucal **1**[11] was chosen as the model reaction to optimize the reaction conditions; the results are summarized in Table 1. When a mixture of compounds **1** and **4** was treated with $Pd(OAc)_2$ (10 mol %) and AgOAc (2 equiv) in toluene at 100 °C, the monoglycosylated product **4a** and diglycosylated product **4aa** were produced in 14 and 47% yields, respectively (entry 1). To obtain the desired monoglycosylated product in high yield and with good selectivity, the effect of base was investigated. Some inorganic bases such as K_2CO_3, Na_2CO_3, and $NaHCO_3$ (entries 2−4) were tried, and it was found that the addition of $NaHCO_3$ increased the ratio of **4a** to **4aa** despite the low yield of **4a**, which might result from the poor solubility of $NaHCO_3$ in toluene. After testing several solvents, we found that when the reaction was conducted in the mixed solvent *t*-AmylOH/H_2O (10:1), the yield of desired product **4a** was doubled and the ratio of **4a** to **4aa** was maintained at 4:1. Previously, Yu's and Chen's work[13,14] showed that the use of ligands could increase the monoselectivity of the reactions. Inspired by these results, we turned our attention to ligand screening. 2,2′-Dipyridyl ($\mathbf{L_1}$) as a ligand was tested. However, the addition of $\mathbf{L_1}$ hindered the reaction, and no products were detected. Following a literature report,[14] when phosphonic acids ($\mathbf{L_2}$, $\mathbf{L_3}$, entries 7 and 8, Table 1) were used, both the overall yield and the monoselectivity of desired product were improved. These results indicated that the use of ligands would truly benefit the reaction. So, we next screened several protected amino acid ligands ($\mathbf{L_4}$−$\mathbf{L_{10}}$, entries 9−15). It was found that the L-proline derivative $\mathbf{L_5}$ was the most effective ligand, leading to the formation of product **4a** in 83% yield and with more than 8:1 selectivity of **4a**/**4aa**.

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	additive (2 equiv)	solvent	yield (%) 4a	4aa
1	--	AgOAc	toluene	14	47
2	--	K_2CO_3	toluene	0	90
3	--	Na_2CO_3	toluene	40	46
4	--	$NaHCO_3$	toluene	24	5
5	--	$NaHCO_3$	A:H=10:1	48	12
6	L_1	$NaHCO_3$	A:H=10:1	--	--
7	L_2	$NaHCO_3$	A:H=10:1	65	14
8	L_3	$NaHCO_3$	A:H=10:1	59	13
9	L_4	$NaHCO_3$	A:H=10:1	75	9
10	L_5	$NaHCO_3$	A:H=10:1	83	10
11	L_6	$NaHCO_3$	A:H=10:1	50	2
12	L_7	$NaHCO_3$	A:H=10:1	67	3
13	L_8	$NaHCO_3$	A:H=10:1	44	3
14	L_9	$NaHCO_3$	A:H=10:1	62	10
15	L_{10}	$NaHCO_3$	A:H=10:1	59	3



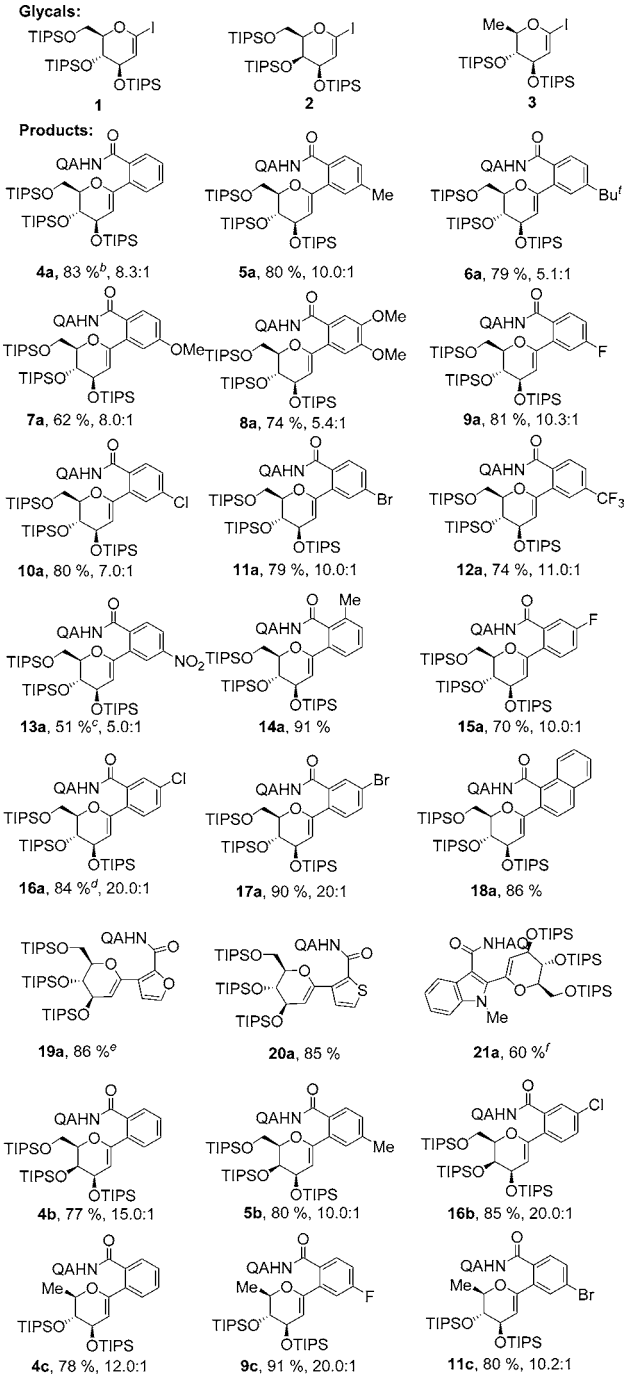
[a]Unless specified, a solution of **4** (0.04 mmol), **1** (0.08 mmol), and the catalyst (0.004 mmol) in *t*-AmylOH/H_2O (0.20 M) was heated at 100 °C for 10 h. Yields are based on ^1H NMR analysis of the crude reaction mixture, using dibromomethane as an internal standard. A = *t*-AmylOH, H = H_2O.

Having the optimized reaction conditions in hand, we evaluated the generality of our method for synthesizing *C*-aryl glycosides by using various substrates, including different glycals and *N*-quinolyl benzamides. The results are shown in Chart 1. When the glucal derivative **1** was used, the reaction of the unsubstituted *N*-quinolyl benzamide (**4**) worked well and the reactions of substituted *N*-quinolyl benzamides bearing either electron-donating groups such as Me, *t*-Bu, MeO, and di-MeO functionalities or electron-withdrawing groups such as F, Cl, Br, CF_3, and NO_2 functionalities proceeded smoothly, furnishing the desired products **4a**−**17a** in moderate to excellent yields and with good selectivity. Halo groups, especially the bromo group, were compatible with the reaction conditions. In addition, different substituents at the *ortho*-, *meta*-, or *para*-positions of the quinolyl benzamides had little influence on the reaction outcomes. 1-Naphthalene-derived amide and other heterocyclic amides as substrates also worked well (the formation of **18a**−**21a**). Besides the glucal **1**, the reactions of glycals **2** and **3** from galactose and rhamnose with different quinolyl benzamides were examined. The coupling reactions of these two glycals with benzamides provided the corresponding products in good yields and with high mono/di ratios (the formation of **4b**, **5b**, **16b**, **4c**, **9c**, **11c**). To further investigate the practical utility of this protocol, the gram-scale preparation of **16a** from **1** was realized in yields up to 93% under the optimized reaction conditions. After validating this method, we tried to deprotect the *N*-quinolyl directing group and synthesize the *C*-aryl glycoside derivatives through modifications of the double bond on the sugar ring and the amide bond of the *N*-quinolyl benzamide moiety. Because of the instability of the silyl group under strong basic and acidic conditions and poor solubility of aryl-*C*-$\Delta^{1,2}$-glycosides in the protic solvents, we failed to convert the amide products to the corresponding acids or esters by using various conditions such as acids and bases in different solvent systems.

The *N*-quinolyl benzamide was then transformed into the hydroxymethyl group by sequential reductions with Schwartz's reagent[15] and $NaCNBH_3$. The amide was first reduced to the aldehyde which was prone to degradation during the purification process. So the aldehyde was either directly treated with triphenylphosphonium benzylide to furnish the stilbene-

DOI: 10.1021/acs.orglett.6b00566
Org. Lett. 2016, 18, 1836−1839

Chart 1. Scope of the Coupling Reactions[a]

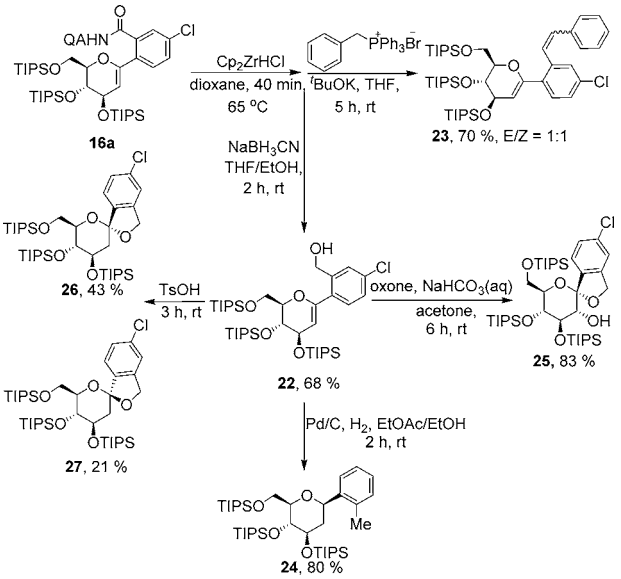


[a]All reactions were carried out on a 0.04 mmol scale, unless specified; isolated yields were given; ratios (mono- versus diglycosylation) were determined by ^{1}H NMR. [b]Reaction was conducted in 0.10 mmol. [c]CH_2Cl_2 as solvent. [d]Reaction was conducted in 1.0 mmol. [e]K_2CO_3 (2 equiv) was used. [f]CH_2Cl_2 as solvent and 20 mol % of $Pd(OAc)_2$ as catalyst.

containing *C*-glycoside **23**[16] in 70% yield or further reduced *in situ* to the hydroxymethyl-containing compound **22** in 68% overall yield (Scheme 2).

Starting from compound **22**, three transformations were effected as follows: (1) When the unsaturated compound **22** was subjected to hydrogenation under a H_2 atmosphere in the presence of Pd/C, the corresponding 2-deoxy-β-*C*-aryl glycoside

Scheme 2. Further Transformations of the Coupled Product



24 was obtained in 80% yield. (2) The epoxidation of **22** using oxone in acetone and subsequent in situ ring opening of the epoxide by the hydroxyl group provided the spiro-cyclization product **25** of the papulacandin skeleton in good yield. (3) Treatment of **22** with *p*-TsOH·H_2O in CH_2Cl_2 at room temperature furnished two spirocyclic isomers **26** and **27** in one step (Scheme 2).[3d,17] It should be mentioned that the stereochemistry of products **25**, **26**, and **27** was confirmed by NMR analysis (NOESY studies, Figure 2).[18]

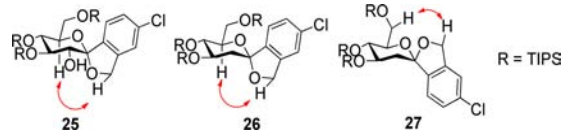
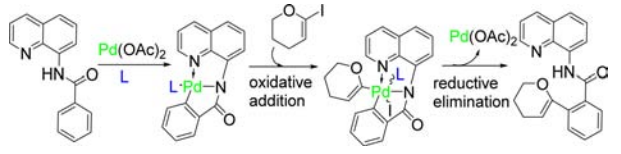


Figure 2. NOESY correlations (red arrows) of compounds **25**, **26**, and **27**.

On the basis of our results and previous reports,[8a,14,19] a plausible C−H activation mechanism is proposed in Scheme 3. 1-

Scheme 3. Proposed Mechanism



Iodoglycal undergoes oxidative addition (OA), which is supposed to be the rate-determining step of C−H functionalization,[20] to give a palladacycle intermediate, generated from the Pd coordination with AQ and insertion between carbon and hydrogen atoms. In our method, amino acid ligands probably coordinate to the palladacycle, which decreases the reaction rate of the first OA and makes the second OA more difficult (time course, Figure S1 in the Supporting Information), leading to the high monoselectivity and good yields of the coupled products. Limiting the amount of $NaHCO_3$ was also important for achieving high monoselectivity and high yield.

DOI: 10.1021/acs.orglett.6b00566
Org. Lett. 2016, 18, 1836−1839

In summary, we have developed a method for the monoselective synthesis of aryl-C-$\Delta^{1,2}$-glycosides via Pd-catalyzed C−H functionalization of *N*-quinolyl benzamides with different types of 1-iodoglycals in a straightforward, atom-economic, and environmentally friendly manner. The monoselectivity of the glycosylation products can be controlled by the addition of amino acid ligands. The reaction can be scaled up, and the protocol can be applied to synthesize natural product derivatives of potential biological importance by simple transformations. The preparation of new compounds with the therapeutic potential by this protocol is currently underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00566.

Experimental procedures and characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wuyanfen@bjmu.edu.cn.
*E-mail: xinshan@bjmu.edu.cn.

Author Contributions

†M.L. and Y.N. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by grants (2012CB822100 and 2013CB910700) from the Ministry of Science and Technology of China, and the National Natural Science Foundation of China (Grant No. 21232002).

■ REFERENCES

(1) (a) Franz, G.; Grun, M. *Planta Med.* **1983**, *47*, 131−140. (b) Humber, D. C.; Mulholland, K. R.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 283−292. (c) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742−760. (d) Lee, D. Y. W.; He, M. S. *Curr. Top. Med. Chem.* **2005**, *5*, 1333−1350. (e) Rich, J. R.; Wakarchuk, W. W.; Bundle, D. R. *Chem. - Eur. J.* **2006**, *12*, 845−858. (f) Gong, H.; Sinisi, R.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908−1909. (g) Anand, N.; Upadhyaya, K.; Ajay, A.; Mahar, R.; Shukla, S. K.; Kumar, B.; Tripathi, R. P. *J. Org. Chem.* **2013**, *78*, 4685−4696. (h) Lalitha, K.; Muthusamy, K.; Prasad, Y. S.; Vemula, P. K.; Nagarajan, S. *Carbohydr. Res.* **2015**, *402*, 158−171.

(2) Li, H. H.; Ye, X. S. *Org. Biomol. Chem.* **2009**, *7*, 3855−3861.

(3) (a) Koester, D. C.; Kriemen, E.; Werz, D. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2985−2989. (b) Dubois, E.; Beau, J.-M. *Tetrahedron Lett.* **1990**, *31*, 5165−5168. (c) Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. J. Chem.* **1994**, *72*, 1262−1272. (d) Parkan, K.; Pohl, R.; Kotora, M. *Chem. - Eur. J.* **2014**, *20*, 4414−4419.

(4) (a) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709−1712. (b) Xiang, S.; Cai, S.; Zeng, J.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 4608−4611. (c) Novoa, A.; Pellegrini-Moïse, N.; Lamandé-Langle, S.; Chapleur, Y. *Tetrahedron Lett.* **2009**, *50*, 6484−6487.

(5) (a) Daves, G. D. *Acc. Chem. Res.* **1990**, *23*, 201−206. (b) Cheng, J. C. Y.; Hacksell, U.; Daves, G. D. *J. Org. Chem.* **1986**, *51*, 3093−3098.

(6) (a) Yu, X.; Dai, Y.; Yang, T.; Gagné, M. R.; Gong, H. *Tetrahedron* **2011**, *67*, 144−151. (b) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177−12183.

(7) (a) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780−1824. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009. (c) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (f) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72.

(8) (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074−1086. (b) Wencel-Delord, J.; Colobert, F. *Chem. - Eur. J.* **2013**, *19*, 14010−14017. (c) Liu, Y. J.; Xu, H.; Kong, W. J.; Shang, M.; Dai, H. X.; Yu, J. Q. *Nature* **2014**, *515*, 389−393. (d) Wang, Y.; Zhou, K.; Lan, Q.; Wang, X. S. *Org. Biomol. Chem.* **2015**, *13*, 353−356. (e) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602−13605. (f) Giri, R.; Thapa, S.; Kafle, A. *Adv. Synth. Catal.* **2014**, *356*, 1395−1411. (g) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588−5598. (h) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (i) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115.

(9) (a) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941−2946. (b) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926−2927. (c) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689−9714. (d) Reddy, B. V.; Reddy, C. R.; Reddy, M. R.; Yarlagadda, S.; Sridhar, B. *Org. Lett.* **2015**, *17*, 3730−3733.

(10) (a) Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952−6953. (b) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149−2152. (c) Huang, Z.; Qian, M.; Babinski, D. J.; Negishi, E.-i. *Organometallics* **2005**, *24*, 475−478.

(11) (a) Denmark, S. E.; Kobayashi, T.; Regens, C. S. *Tetrahedron* **2010**, *66*, 4745−4759. (b) Potuzak, J. S.; Tan, D. S. *Tetrahedron Lett.* **2004**, *45*, 1797−1801.

(12) We screened several other directing groups such as *N*-(pivaloyloxy)benzamide, *N*-phenylpivalamide, *N*-methoxy benzamide, benzoic acid derivative, picolinic acid derivative, and *N*-quinolyl benzamide, and *N*-quinolyl benzamide was found to be the most efficient directing group for the C−H activation and subsequent glycosylation by TLC detection.

(13) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J. Q. *Nat. Chem.* **2014**, *6*, 146−150.

(14) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531−539.

(15) Yi, J.; Yang, L.; Xia, C.; Li, F. *J. Org. Chem.* **2015**, *80*, 6213−6221.

(16) Wang, Y. H.; Zhang, Z. K.; He, H. P.; Wang, J. S.; Zhou, H.; Ding, M.; Hao, X. J. *J. Asian Nat. Prod. Res.* **2007**, *9*, 631−636.

(17) (a) Wurst, J. M.; Liu, G.; Tan, D. S. *J. Am. Chem. Soc.* **2011**, *133*, 7916−7925. (b) Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, *5*, 2405−2408. (c) Sakamaki, S.; Kawanishi, E.; Nomura, S.; Ishikawa, T. *Tetrahedron* **2012**, *68*, 5744−5753. (d) Potuzak, J. S.; Tan, D. S. *Tetrahedron Lett.* **2004**, *45*, 1797−1801.

(18) (a) Mainkar, P. S.; Johny, K.; Rao, T. P.; Chandrasekhar, S. *J. Org. Chem.* **2012**, *77*, 2519−2525. (b) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406−4440.

(19) (a) Dang, Y.; Qu, S.; Nelson, J. W.; Pham, H. D.; Wang, Z. X.; Wang, X. *J. Am. Chem. Soc.* **2015**, *137*, 2006−2014. (b) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911−11934. (c) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (d) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191−206. (e) Aihara, Y.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 15509−15512. (f) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743.

(20) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434−442.

DOI: 10.1021/acs.orglett.6b00566
Org. Lett. 2016, 18, 1836−1839