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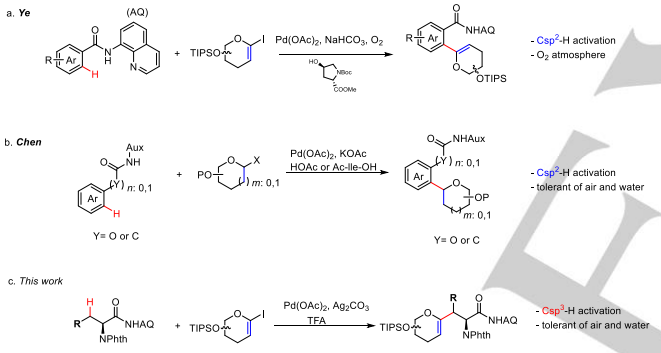
Palladium-Catalysed C(sp^3)-H Glycosylation for Synthesis of *C*-Alkyl Glycoamino Acids

Yichu Liu,[a,b,c] Yibing Wang,[b,c] Wenhao Dai,[b,c] Wei Huang,[b,c] Yingxia Li*[a] and Hong Liu*[b,c]

Abstract: In this work, we developed a highly efficient and practical approach for the palladium-catalyzed trifluoroacetate-promoted *N*-quinolylcarboxamide-directed glycosylation of inert *β*-C(sp^3)-H bonds of *N*-phthaloyl *α*-amino acids with glycals under mild conditions. For the first time, the C(sp^3)-H activation for glycosylation was achieved to build *C*-alkyl glycosides. This method facilitates the synthesis of various *β*-substituted *C*-alkyl glycoamino acids and offers a tool for glycopeptide synthesis.

C-glycosides exhibit enhanced *in vitro* and *in vivo* stability compared with *O*- or *N*-glycosides and therefore become an attractive strategy for structural optimization in carbohydrate-based drugs development[1]. For instance, the design of SGLT2 inhibitors, replacement of *O*-glycoside with *C*-glycoside can dramatically improve the pharmacokinetic profiles and drug-like property[2]. Glycoamino acids, as mimic moieties of protein glycosylation, represent a featured scaffold and building block for regulating carbohydrate-mediated biological events[3].

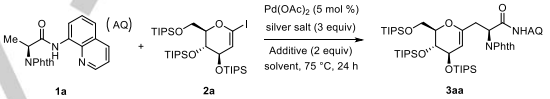
Scheme 1. Approaches to access *C*-glycosides *via* C-H functionalization.



Over the past few decades, the synthesis of complex *C*-glycosides has achieved significant progress. However, many existing methods resort to pre-functionalized coupling partners of high reactivity (such as metallation arenes/alkanes for nucleophilic substitution and metal-catalysed cross-coupling)[4], lack the general regiochemical control (such as the Friedel-Crafts-type glycosylation)[5], and often require a multi-step reaction sequence and delicate operating conditions[6]. Recently, several groups reported elegant methods for the synthesis of *C*-aryl glycosides *via* C-H functionalization[6-7], which applied metal-catalyzed activation of aryl C-H bond and avoided preactivation of the acceptors in glycosylation. These methods offer a mild, straightforward, efficient and general strategy for the synthesis of a series of *C*-aryl glycosides. Nevertheless, these approaches are highly useful for C(sp^2)-H but not for the less active C(sp^3)-H. Therefore, developing C(sp^3)-H activation for the synthesis of *C*-alkyl glycosides would be highly valuable.

Here, we report a simple and powerful strategy for the regio- and diastereoselective synthesis of *C*-alkyl glycoamino acids *via* Pd-catalysed, *N*-quinolyl-group-directed *β*-C(sp^3)-H functionalization of natural and unnatural *α*-amino acids with readily accessible 1-iodoglycals (Scheme 1c). This work facilitates the synthesis of various *C*-glycoamino acids with structural diversity, and more importantly, it presents a general strategy for *C*-alkyl glycosides synthesis *via* C(sp^3)-H activation which will advance the state-of-the-art technique in carbohydrate chemistry.

Table 1. Optimization of the reaction conditions[a]



1a 2a 3aa

Entry	Silver salt	Additive	Solvent	Yield (%) [b]
1	AgOAc	-	Toluene	10
2	Ag_2CO_3	-	Toluene	18
3	AgOTf	-	Toluene	0
4	Ag_2O	-	Toluene	0
5	$AgBF_4$	-	Toluene	0
6	AgTFA	-	Toluene	45
7	AgOAc	$(BnO)_2PO_2H$	Toluene	23
8	Ag_2CO_3	$(BnO)_2PO_2H$	Toluene	48
9	AgTFA	$(BnO)_2PO_2H$	Toluene	56
10	AgOAc	TFA	Toluene	30
11	Ag_2CO_3	TFA	Toluene	61
12	Ag_2CO_3	TFA	DCE	52
13	Ag_2CO_3	TFA	THF	88
14	Ag_2CO_3	TFA	t-AmylOH	43
15	Ag_2CO_3	TFA	1,4-dioxane	68
16	Ag_2CO_3	TFA	Acetone	39
17	Ag_2CO_3	TFA	THF	58[c]
18	Ag_2CO_3	TFA	THF	76[d]

[a] Reaction conditions: **1a** (0.04 mmol), **2a** (0.08 mmol), $Pd(OAc)_2$ (5 mol%), silver salt (0.12 mmol), and an additive (0.08 mmol) were stirred in a solvent (2 mL) at 75 °C for 24 h. [b] Yield of isolated products. [c] Reaction temperature 60 °C. [d] Reaction temperature 90 °C.

Initially, *N*-phthaloyl Alanine **1a** and triisopropylsilyl-protected 1-iodoglucal **2a** were used as the glycosylation acceptor and donor substrates respectively for the optimization of reaction conditions. Although aminoquinoline (AQ) is extensively used as the directing group in C-H activation, great challenge still remains for its application in glycosylation which is extremely sensitive to moisture and oxygen. We focused on screening various silver salts as the additive by employing $Pd(OAc)_2$ (5 mol%) as a catalyst at 75 °C stirred in toluene for 24 h. The results are summarized in Table 1. As shown in Table 1, the reaction occurred when in the presence of AgOAc, Ag_2CO_3 or AgTFA, affording the desired product **3aa** in low yield (entry 1, 2,

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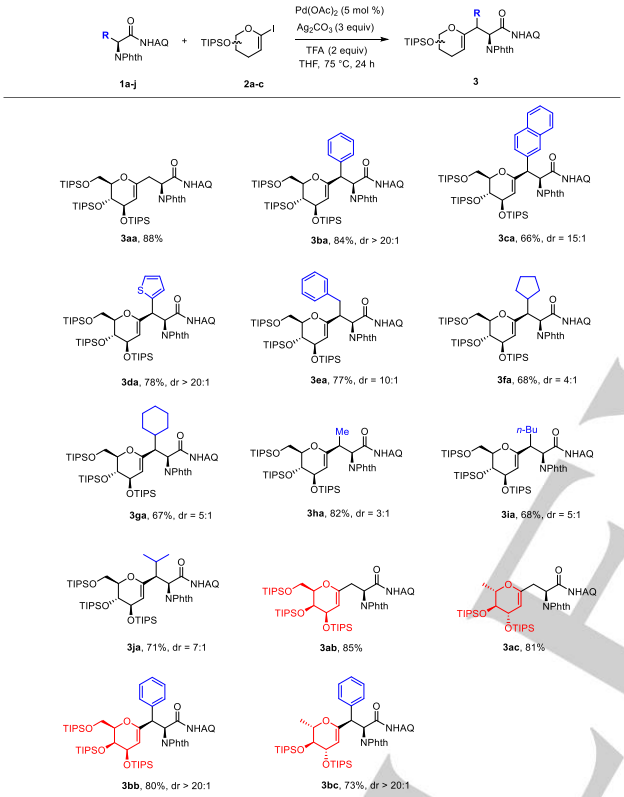
and 6). Previously, Chen's work showed that using TFA or $(BnO)_2PO_2H$ as additive could increase the yield of the products[8]. To our delight, the results demonstrated that employing combination of Ag_2CO_3 and TFA could moderately increase the yield of **3aa** to 61% (Table 1, compare entries 7-10 with 11). Subsequently, we continued to evaluate various solvent to further improve the reaction conversion of **1a** (Table 1, entries 12-16). Among the investigated solvents, THF was identified as the optimal solvent that could significantly improve the yield of **3aa** from 61% to 88%. It should be noted that lowering or increasing the reaction temperature led to worse results (Table 1, compare entries 17-18 with 13).

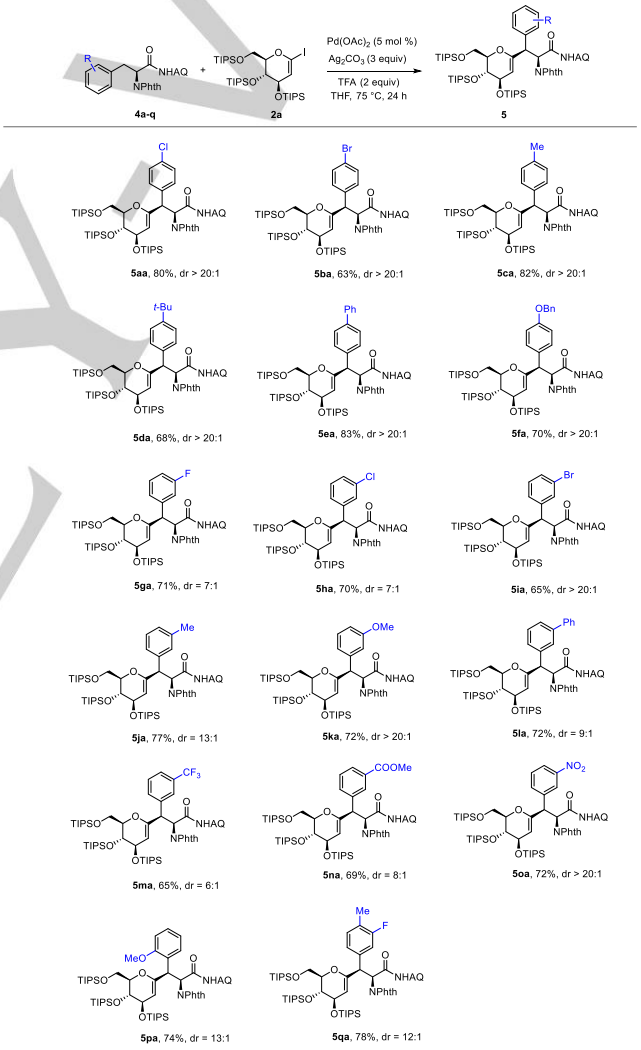
Scheme 2. Scope of 1-iodoglycals and α-amino acids.



The excellent yield after successful condition optimization encouraged us to further examine the substrate scope of this method, using **2a** with various *N*-phthaloyl α-amino acid substrates **1** under the general conditions using Ag_2CO_3 (2 equiv)/TFA (3 equiv). The results are shown in Scheme 2. As expected, *N*-phthaloyl Phenylalanine **1b** with a secondary C-H bond successfully generated the product **3ba** with 84% yield and excellent diastereoselectivity (dr > 20:1) (the dr value is estimated by ^{1}H NMR, see Supporting Information). Moreover, the reactions of β-substituted α-amino acids tolerating functional groups such as aryl (**3ba**-**3ea**), cycloalkyl (**3fa** and **3ga**), linear alkyl (**3ha** and **3ia**), and branched alkyl (**3ja**) proceeded smoothly, furnishing the desired products **3ba-3ja** in moderate to good yields and with acceptable diastereoselectivity (dr = 20:1 ~ 3:1). Notably, the lower diastereoselectivity of **3ha** is presumably due to the less steric hindrance between methyl and phthalimide. Besides the glucal **2a**, the reactions of glycals **2b** and **2c**, respectively derived from galactose and rhamnose, with *N*-phthaloyl Alanine **1a** and *N*-phthaloyl Phenylalanine **1b** also worked well (Scheme 2, **3ab-3bc**).

Finally, the scope of the present procedure with regard to different types of *N*-phthaloyl Phenylalanine derivatives **4** has also been established systematically (Scheme 3). A variety of functional groups, either electron-donating groups (Me, *t*-Bu, Ph, BnO, and MeO) or electron-withdrawing groups (F, Cl, Br, CF_3, COOMe, and NO_2), were well tolerated. In addition, most reactions using substrate **4** bearing different substituents at either *ortho*- or *meta*-positions of the phenyl ring had good diastereoselectivity (dr = 20:1 ~ 6:1). In contrast, excellent diastereoselectivity was achieved when the substituents were at *para*-positions (**5aa-5fa**, dr > 20:1), possibly because of less steric hindrance between R group and iodine atom.

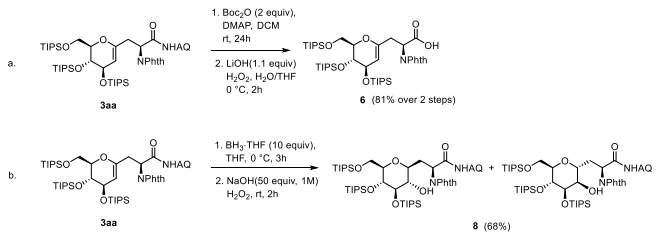
Scheme 3. Scope of *N*-phthaloyl Phenylalanine derivatives.



To highlight the synthetic utility of this procedure, further transformations of the products were performed (Scheme 4). As shown in Scheme 4a, the directing group can be smoothly removed under mild reaction conditions. Amide-linked AQ group was cleanly cleaved *via* a two-step sequence of Boc activation and LiOH cleavage to give a free carboxylic acid **6** in excellent yield. As the hydroxyl protecting group, TIPS group can be

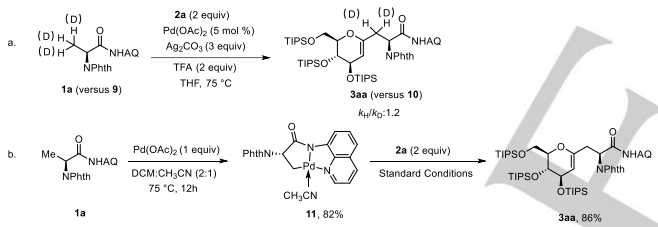
removed by TBAF in tetrahydrofuran (details see Supporting Information Scheme S5). Furthermore, the glucal can be successfully converted to glucose by hydroboration-oxidation reaction (Scheme 4b).

Scheme 4. Further transformations of the product.



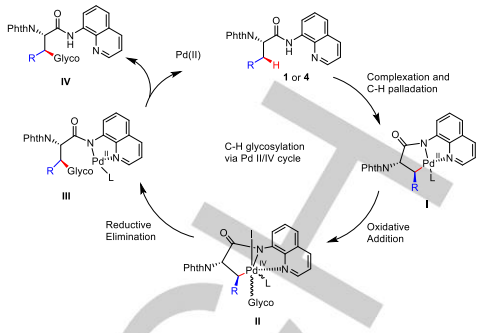
As shown in Scheme 5a, a small deuterium kinetic isotope effect (KIE) experiments with *N*-phthaloyl Alanine **1a** and **9** (**1a** with deuterated methyl) (k_H/k_D:1.2) indicated that the sp^3 C-H bond cleavage may be not the rate-limiting step in this Pd catalytic cycle[8a]. To get a better understanding of the glycosylation process, a palladacycle **11** was prepared from substrate **1a** *via* C(sp^3)-H activation (Scheme 5b). We found this palladacycle is a fully competent catalyst for reaction of *N*-phthaloyl Alanine **1a** with 1-iodoglucal **2a** under standard conditions. Reaction of **11** with **2a** in THF at 75 °C gave product **3aa** in high yield (Scheme 5b).

Scheme 5. Mechanistic investigation.



On the basis of the above results and previous reports[7-9], a plausible C-H activation mechanism was proposed. As shown in Scheme 6, the palladacycle **I** was firstly generated *via* cyclometallation. This palladacycle intermediate provided us a reliable model to predict the diastereoselectivity of the *β*-glycosylations[8b,10]. Then the oxidative addition of **I** with 1-iodoglycal afforded the intermediate **II**, which underwent reductive elimination to afford intermediate **III**. Subsequently, **III** underwent disassociation to generate the desired product **IV** and release Pd catalyst. The exact role of a carboxylic acid additive such as TFA is unclear at the moment. To account for the unusual reactivity, trifluoroacetate may serve as a unique ligand to stabilize the Pd(II) palladacycle intermediate **I** or even facilitate the oxidative addition[6, 8a].

Scheme 6. Proposed mechanism.



In summary, we have developed a highly efficient and practical protocol for the palladium-catalyzed trifluoroacetate-promoted *N*-quinolylcarboxamide-directed glycosylation of unactivated *β*-C(sp^3)-H bonds of *N*-phthaloyl amino acids with glycals under mild conditions. To the best of our knowledge, this is the first time to build *C*-alkyl glycoamino acids by C-H activation. Glycals can be regio- and stereoselectively installed onto the *β*-position of a broad range of AQ-coupled *N*-phthaloyl amino acids to provide various natural and unnatural *C*-alkyl glycoamino acid compounds. From an operational perspective, these glycosylation reactions are compatible with sensitive functional groups, tolerant of air and water, and suitable for gram scale synthesis (see Supporting Information 3.1 Scale-up Reaction). Moreover, a palladacycle has been successfully prepared to elucidate the mechanism of this *β*-C(sp^3)-H glycosylation process. We anticipate that this protocol will provide an opportunity to access various *β*-substituted *C*-alkyl glycoamino acids, difficult to be obtained by other means, in a diastereoselective and programmable manner.

Acknowledgements

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Keywords: *C*-alkyl glycosides • C(sp^3)-H activation • *α*-amino acids • palladium • diastereoselectivity

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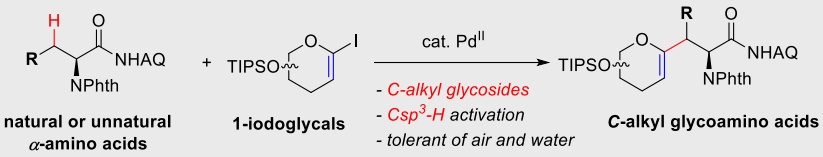

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Palladium-Catalysed C(sp³)-H Glycosylation for Synthesis of *C*-Alkyl Glycoamino Acids

This work initially presents a general strategy for *C*-alkyl glycosides synthesis *via* C(sp³)-H activation which will advance the state-of-the-art technique in carbohydrate chemistry.