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Palladium-Catalyzed Glycosylation: Novel Synthetic Approach to Diverse *N*-Heterocyclic Glycosides

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Supporting Information

ABSTRACT: An efficient and highly stereoselective method for the construction of *N*-heterocyclic glycosides is reported. This method is based on a palladium-catalyzed allylation which proceeded to provide *N*-heterocyclic glycosyl compounds in good-to-excellent yields with β- or α-selectivity. Various *N*-nucleophiles were examined for this reaction and selected *N*-glycosyl isatin substrates were further elaborated to bis-indole sugars which have potential as antiproliferative drugs.

N-Heterocyclic glycosides and glycoconjugates widely exist in many natural products and play significant roles in many biological processes.[1] Nucleosides, in particular, possess great potential as antitumor and antiviral drugs due to their functionality manipulating genetic processes involving *N*-glycosidic linkages.[2] Due to their biological importance, nucleosides have attracted much attention. With the development of glycobiology, an increasing number of *N*-glycosylated heterocycle-containing structures, such as Akashine A[3] and Staurosporine,[4] have been found to be valuable in the pharmaceutical field (Figure 1). Moreover, the activities of some other bioactive natural products such as bis-indole-occurring compounds can be significantly increased by incorporating a sugar moiety through an *N*-glycosidic bond.[5] However, to date, there are very few synthetic methods to construct this kind of glycosidic linkages.[6] Transition metals have demonstrated their catalytic capability for the formation of C−N bonds with high efficiency and selectivity.[7] Among them, palladium is the most widely used catalyst, and many good methods for C−N bonds formation are based on palladium-catalyzed reactions.[8]

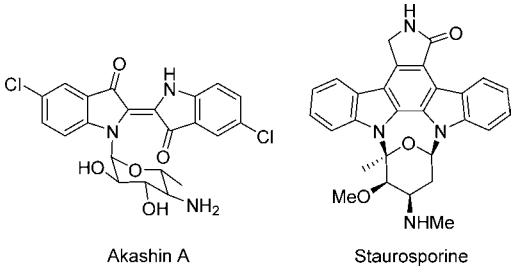

Figure 1. Natural products containing *N*-glycosylated bis-indole structure.

For *N*-heterocyclic glycosylation, we preferred glycal type donors since the coordination between the palladium catalyst and the double bond in the sugar ring could potentially lead to improved stereoselectivity through a classic Ferrier rearrangement and provide versatile synthetic building blocks for further functionalization.[9] The difficulties of generating Pd-π-allyl intermediates and their poor reactivities as glycosyl donors have limited the development of palladium-catalyzed glycosylation.[10] The trifluoroacetyl group,[11] which can increase the reactivity of the donor by acting as a good leaving group, was therefore introduced to solve these problems. Meanwhile, various coordinating groups such as imidate[12] and cyano[13] are widely used to exert stereocontrol in glycosylations while a picoloyl group offers an alternative for glycosylation as a good leaving and directing group.[14] Our group has been focusing on palladium-catalyzed glycosylation from glycal derivatives for years, and various acceptors have been successfully employed to construct different types of glycosidic bonds with a Pd-π-allyl intermediate as the donor.[8f,15] As a further expansion of this strategy, herein, we report a palladium-catalyzed glycosylation reaction involving diverse *N*-heterocyclic nucleophiles including isatins, imides, and imidazole analogues.

In our initial attempts, a model study was conducted using compounds **1a** as the glycosyl donor and **2a** as the acceptor with $Pd(PPh_3)_4$ as the catalyst. Reaction optimization was first carried out by screening various ligands in anhydrous acetonitrile at 70 °C, and the results are depicted in Table 1. Among the ligands we examined, JohnPhos, SPhos, and

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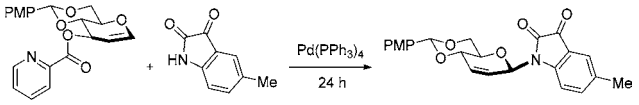
Table 1. Optimization of the Reaction Conditions with Isatin Acceptor[a]



1a 2a 3a

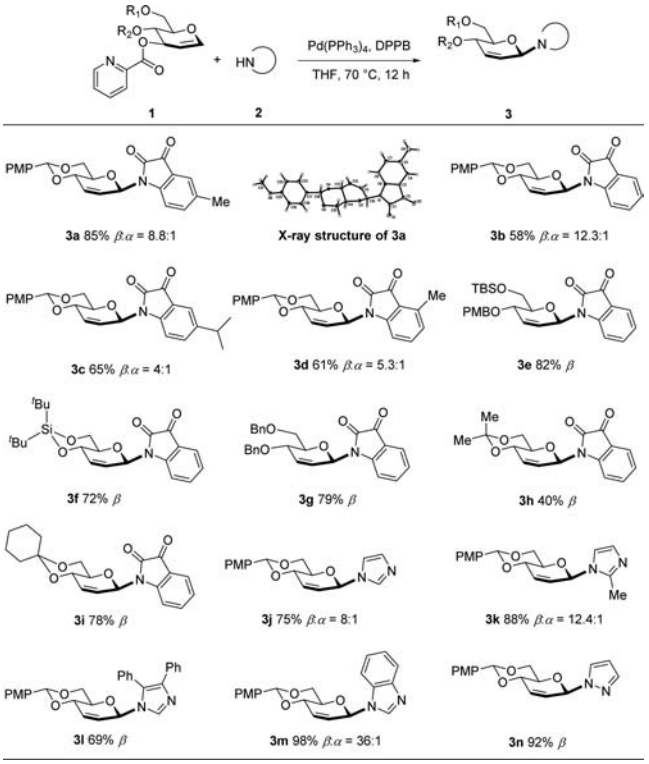
entry	ligand	solvent	temp (°C)	yield (%)[b]	β:α[c]
1	JohnPhos	CH_3CN	70	–	–
2	SPhos	CH_3CN	70	–	–
3	DPPF	CH_3CN	70	35	6:1
4	RuPhos	CH_3CN	70	–	–
5	DPPB	CH_3CN	70	50	9:1
6	DPPB	toluene	70	39	N.D.
7	DPPB	toluene	reflux	42	7:1
8	DPPB	CH_2Cl_2	reflux	12	N.D.
9	DPPB	THF	70	87	8.8:1
10[d]	DPPB	THF	70	85	8.8:1

[a]Unless otherwise specified, all reactions were carried out with 0.1 mmol of **1a**, 0.2 mmol of **2a**, 10% $Pd(PPh_3)_4$, 20% DPPB in 3 mL of solvent for 24 h. [b]Isolated yield. [c]All the ratios were determined by ^1H NMR. [d]The reaction was carried out for 12 h.

RuPhos failed to catalyze this reaction (entries 1, 2, and 4), while DPPF successfully furnished the desired *N*-glycosylation product in 35% yield with incomplete conversion of **1a** (entry 3). DPPB was found to be the best ligand to afford a 50% yield after 24 h with incomplete conversion of starting material (entry 5). The stereoselectivity observed from crude ^1H NMR was β:α = 9:1. The major isomer could be easily purified by column chromatography, and the stereochemistry of the anomeric center was confirmed by X-ray diffraction crystallographic analysis.[16] In our attempts to improve the yield, the solvents were screened. Poor yields were obtained when the reactions were carried out in toluene at both 70 °C and reflux conditions due to the poor solubility of the reactants (entries 6 and 7). CH_2Cl_2 was also unable to give a good yield (entry 8). To our delight, the yield was improved significantly when THF was used (entry 9). Reducing the reaction time from 24 to 12 h resulted in no significant change in the yield (entry 10). Therefore, the optimized reaction conditions were concluded as follows: the reaction was performed with compound **1a** (1.0 equiv) and isatin **2a** (2.0 equiv) in the presence of $Pd(PPh_3)_4$ (0.1 equiv) and DPPB (0.2 equiv) in THF at 70 °C for 12 h.

With the optimized reaction conditions in hand, we proceeded to examine the scope and limitations of this method. The results are summarized in Scheme 1. A range of isatin nucleophiles with various substituents on the aromatic ring were screened. The reaction with an unsubstituted isatin resulted in better selectivity, albeit lower yield (**3b**). When we employed other isatins bearing electron-donating groups, good yields were obtained, with slightly diminished selectivities (**3c**, **3d**). Isatins bearing electron-withdrawing groups, such as 5-Cl, 5-NO_2, or 5-CF_3, were also screened, but they failed to give the desired *N*-glycosides. Next, we synthesized various glycosyl donors to examine the effect of protecting groups. Exclusive β-selectivities were detected with moderate-to-good yields when electron-donating protecting groups were used (**3e**–**3i**). We further employed our reaction conditions for other types of *N*-nucleophiles. Imidazole and its derivatives were then investigated to further expand the substrate scope. When compound **1a** was utilized as the donor, imidazole, 2-methylimidazole, 4,5-diphenylimidazole, benzimidazole, and

Scheme 1. Substrate Scope of *N*-Glycosylation with Glucal Donors[a,b,c]



[a]Unless otherwise specified, all reactions were carried out with 0.1 mmol of **1**, 0.2 mmol of **2**, 10% $Pd(PPh_3)_4$, 20% DPPB in 3 mL of THF at 70 °C for 12 h. [b]Isolated yield. [c]All the ratios were determined by ^1H NMR.

pyrazole successfully provided the corresponding *N*-glycosides in good yields and excellent selectivities (**3j**–**3n**).

Later on, we employed α-type 2,3-unsaturated hexopyranoside **1′**[17] as the donor,[8a] which proved to be effective in achieving the desired α-*N*-glycosides (Scheme 2). Exclusive α-selectivities were obtained in all reactions (**3′a**–**3′d**) with compound **1′** as the starting material, and the stereochemistry of compound **3′c** was confirmed by X-ray diffraction crystallographic analysis.[18]

On the basis of experimental results, the plausible reaction mechanism was outlined in Scheme 3. Initially, palladium coordinated simultaneously to the nitrogen of the picoloyl group as well as the double bond of glucal at the β-face to generate intermediate **II** (Scheme 3a). Next, cleavage of the picoloyl acid species afforded the Pd-π-allyl system as shown in intermediate **III**. Subsequent coordination of the *N*-nucleophile to the palladium released the picoloyl acid giving intermediate **IV** accordingly.

Finally, the β-*N*-glycoside was yielded through an intramolecular nucleophilic addition. Meanwhile, the palladium catalyst **I** was regenerated to complete the reaction cycle. When α-type 2,3-unsaturated hexopyranoside **1′** was employed as the donor, the key intermediate was formed with α-orientation by a double coordination of palladium to compound **1′** (Scheme 3b). The α-isomer was generated by a similar pathway.

In order to demonstrate the applicability of our method, *N*-glycosylated isatins were chosen as precursors to construct the indirubin analogues.[5c] Potentially biological active *N*-glycosy-

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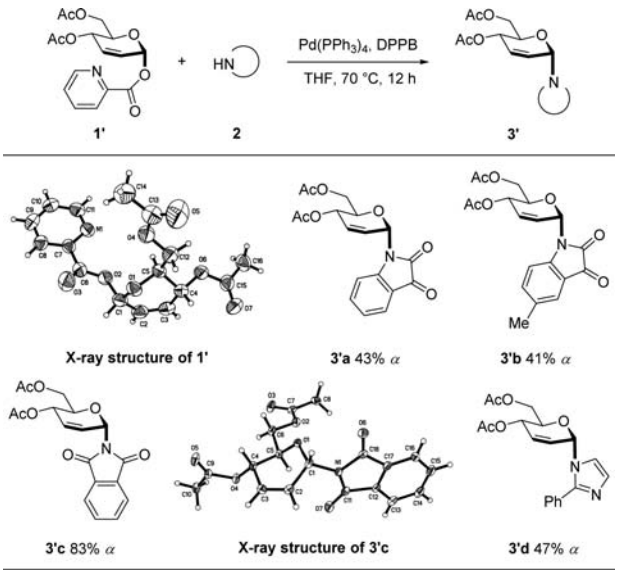
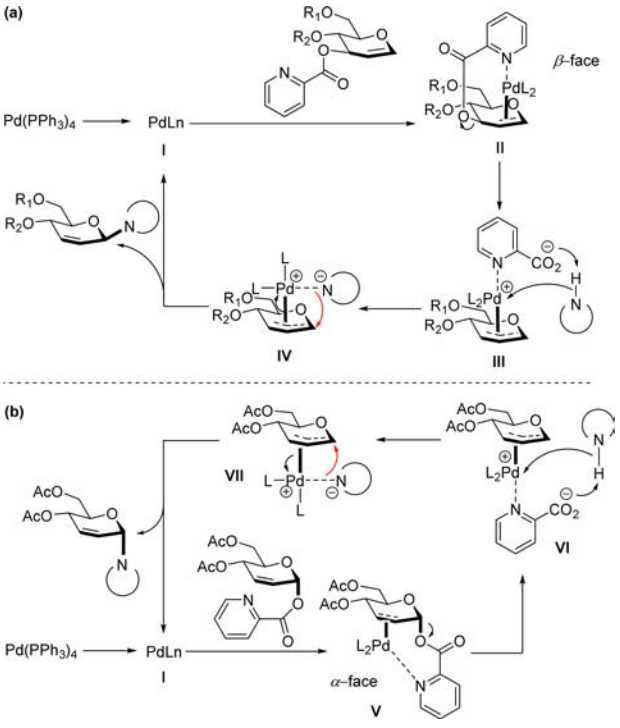
Scheme 2. Substrate Scope of *N*-Glycosylation with Hexopyranoside Donor[a,b,c,d]



[a]Unless otherwise specified, all reactions were carried out with 0.1 mmol of **1′**, 0.2 mmol of **2**, 10% $Pd(PPh_3)_4$, 20% DPPB in 3 mL of THF at 70 °C for 12 h. [b]Isolated yield. [c]All the ratios were determined by ^{1}H NMR. [d]Compound **1′** is unstable even stored at −20 °C.

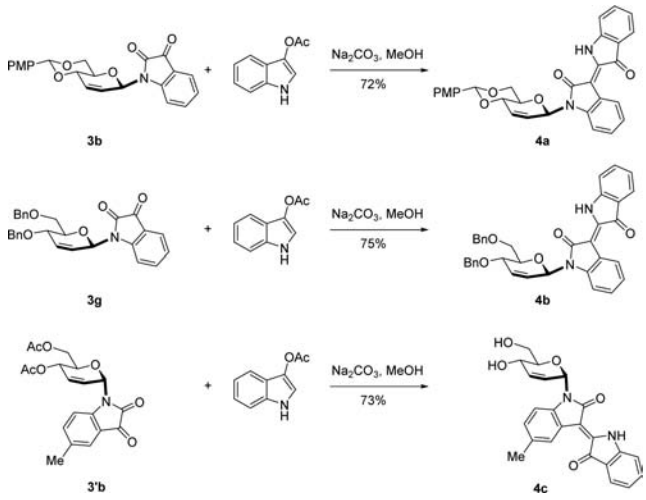
Scheme 3. Plausible Mechanism for the Synthesis of *N*-Glycosides



lated indirubins **4a**, **4b**, and **4c** were successfully synthesized in good yields (Scheme 4).

In conclusion, we have successfully developed an efficient methodology for the stereoselective synthesis of *N*-heterocyclic glycosides. This strategy is based on a palladium-catalyzed allylation reaction with various *N*-nucleophiles. Glucal and α-type 2,3-unsaturated hexopyranoside donors equipped with the *O*-picoloyl group successfully furnished the corresponding β- and α-anomers, respectively. Glycosyl donors with different kinds of protecting groups and a wide variety of glycosyl acceptors such as isatins, imides, and imidazole derivatives were screened. Most of the substrates could yield the desired products in good-to-excellent yields and stereoselectivities. The applicability of our methodology was demonstrated by synthesizing the glycosylated indirubins, which are potent inhibitors toward various kinases.[5]

Scheme 4. Synthesis of Indirubin *N*-Glycosides 4a, 4b, and 4c



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, copies of NMR spectra (for new compounds), and X-ray crystallographic data of **3a**, **1′**, and **3′c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) For more details, see CCDC number 1047594.
(18) For more details, see CCDC number 1047605.

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